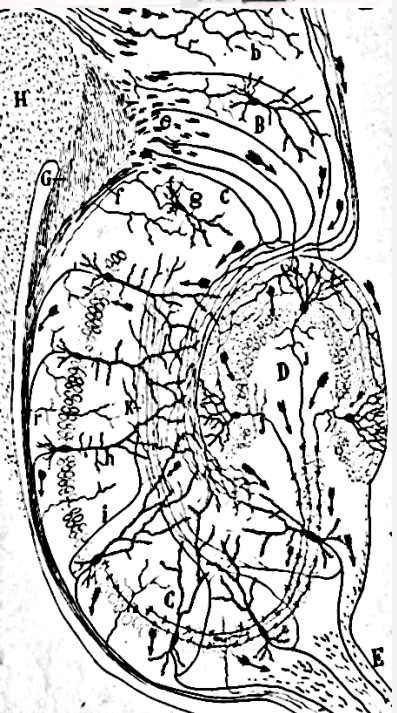


Epilepsy in Pregnancy

P. Emanuela Voinescu, MD, PhD

Brigham and Women's Hospital

Harvard University

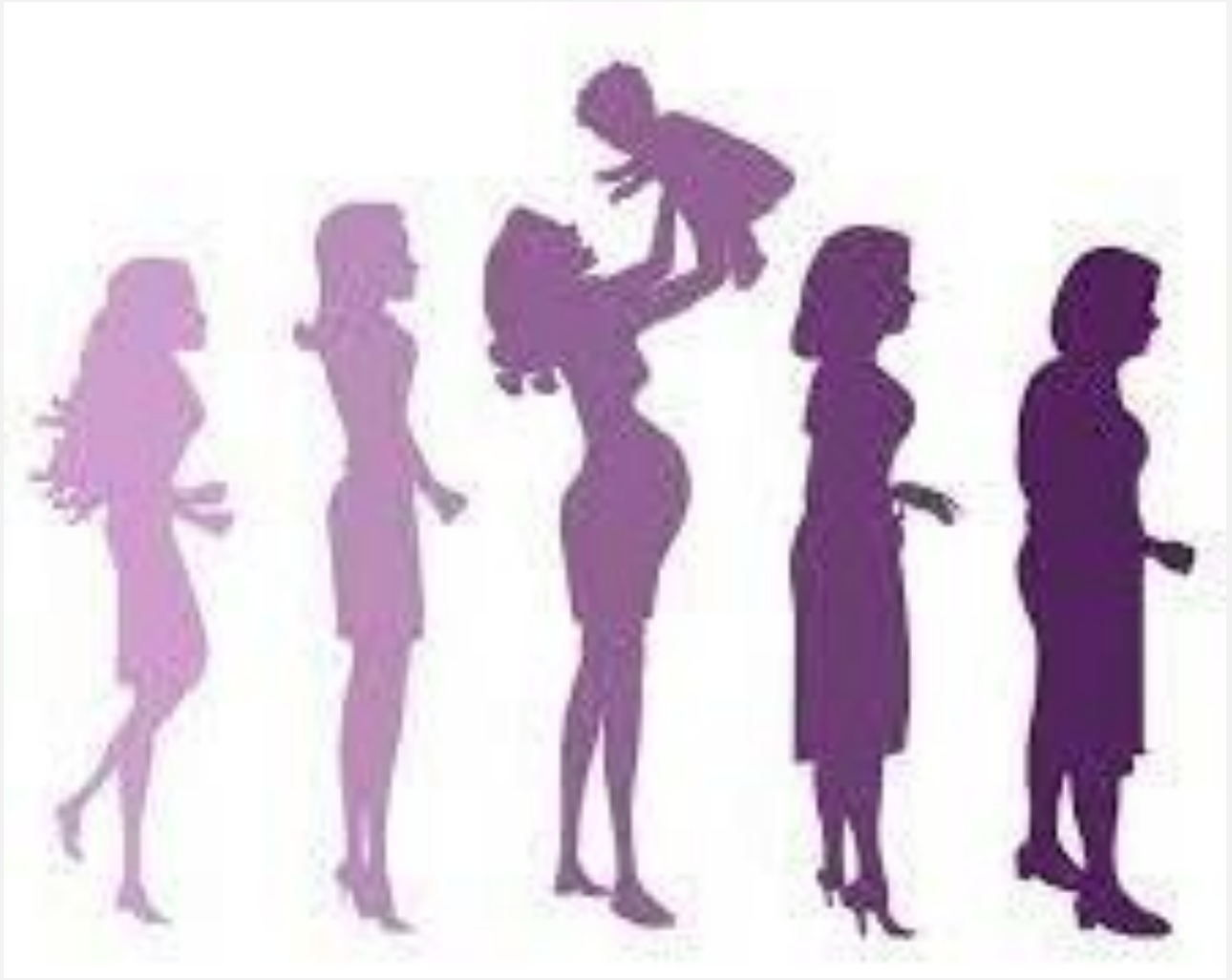
Update on Neurology and Psychiatry of Women

May 9, 2025

Disclosures

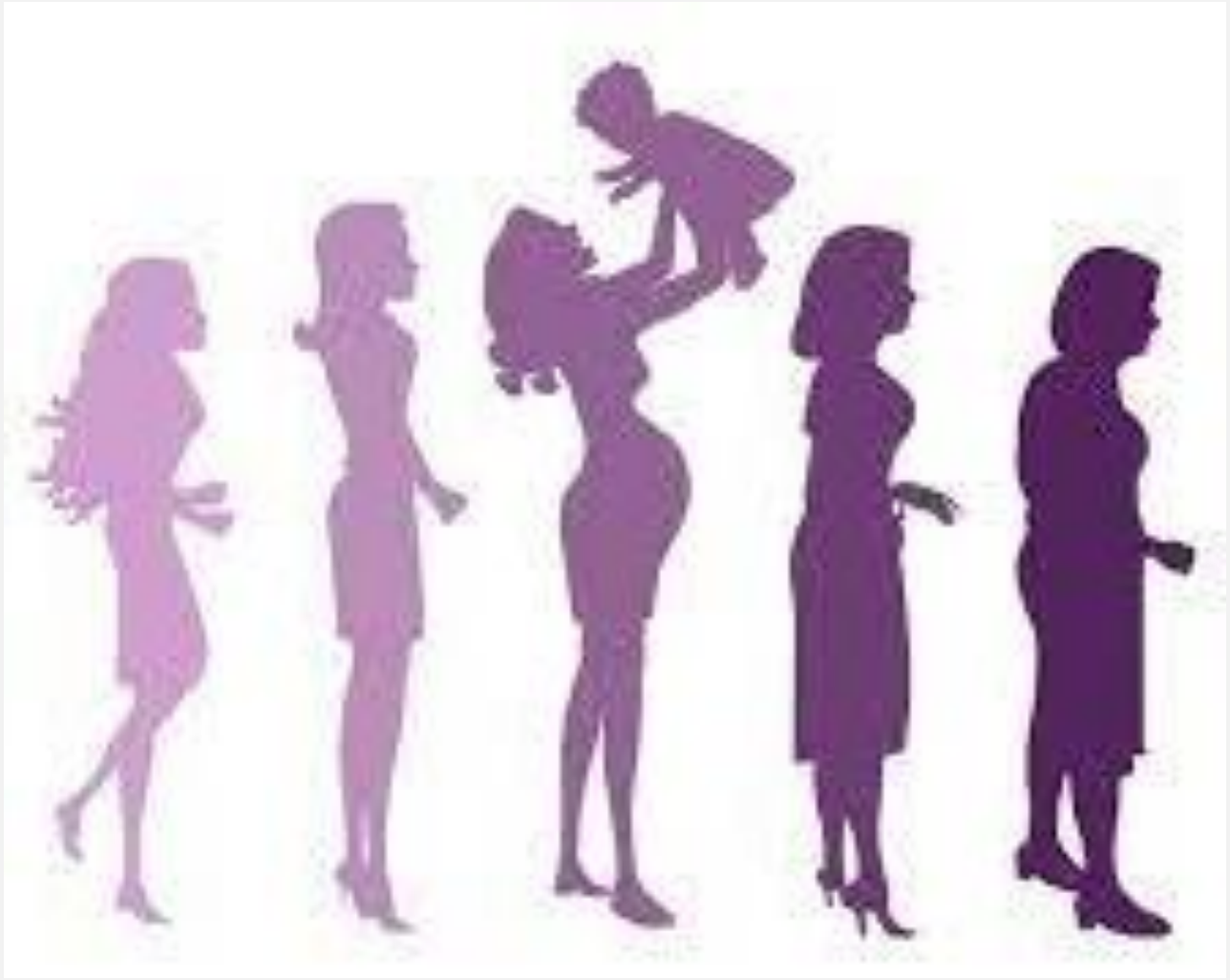
- Board Chair of My Epilepsy Story, a non-profit organization for women with epilepsy
- Member of the Scientific Advisory Board for the North American AED Pregnancy Registry
- Member of the Professional Advisory Board of the Epilepsy Foundation of New England
- Founder of ECAM (Epilepsy in the Childbearing Ages through Menopause) Consortium
- Honoraria for:
  - PhD Opponent for Håkon Vegrim's PhD thesis defense at University of Bergen, Norway
  - Presenter at Philippines League Against Epilepsy

Personalized Care for Women at Different Biological Stages



Contraception
Fertility
IVF/ART
Pregnancy/Postpartum
Catamenial Epilepsy
Perimenopause
Menopause

Personalized Care for Women at Different Biological Stages



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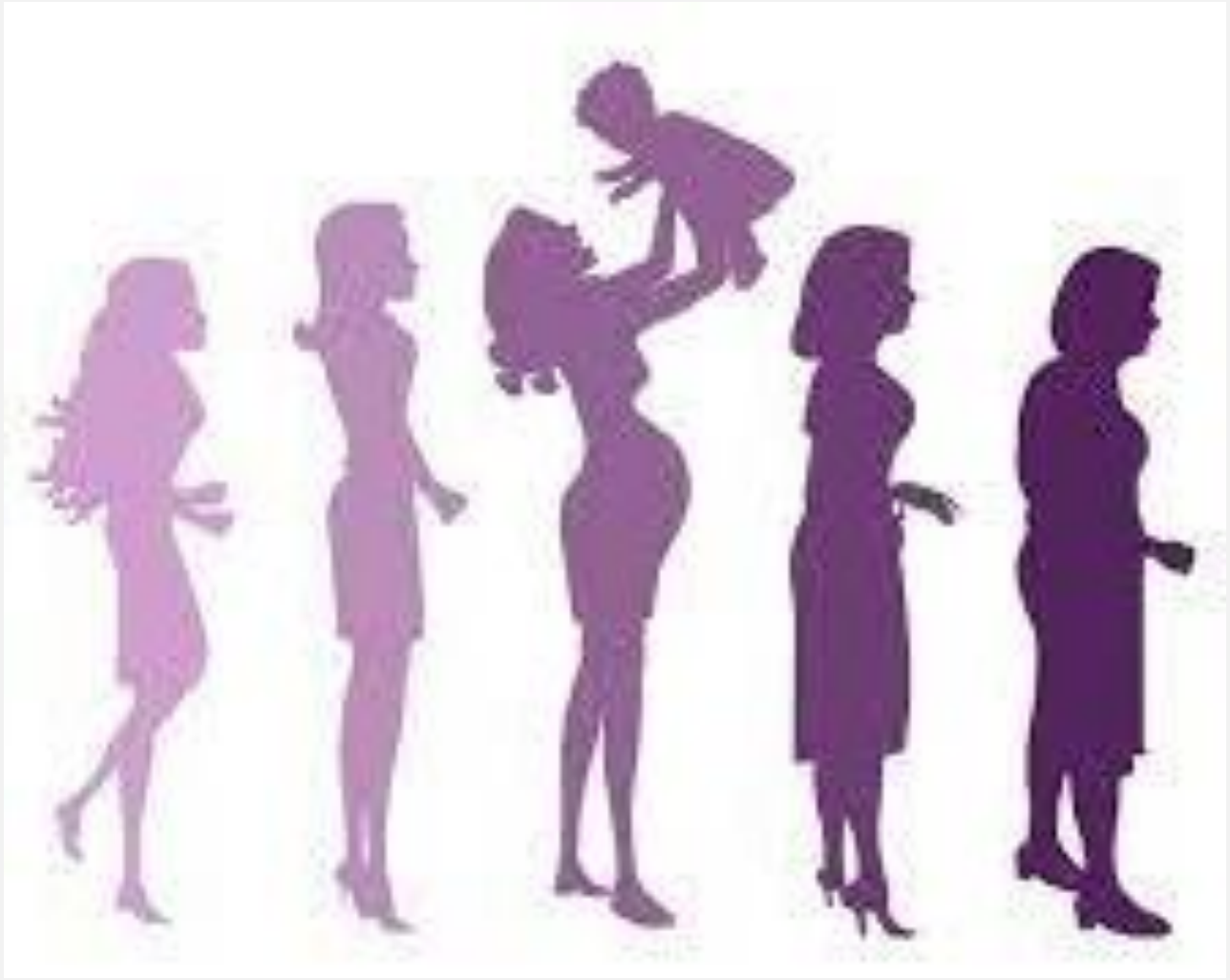

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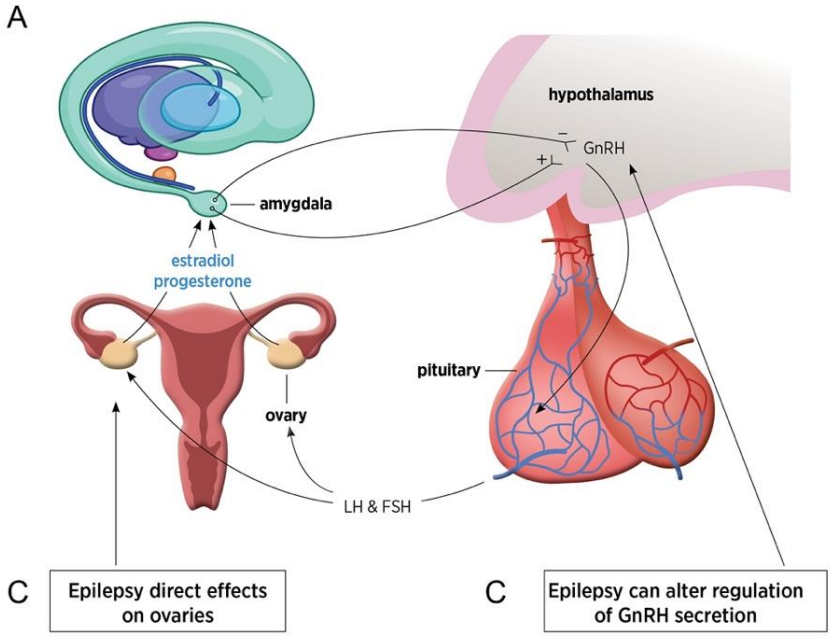

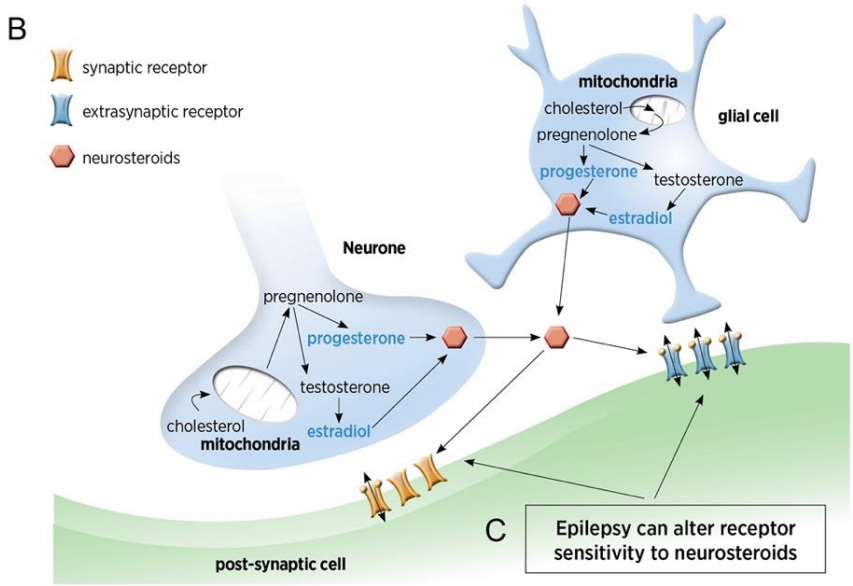

Vadlamudi L and Voinescu PE, *Front Glob Womens Health*. 2024;5:1363470.

The Effect of ASMs and Seizures on Reproductive Function

- Can seizures disrupt the hypothalamic-pituitary gonadal axis?
  - A study of small n WWE with TLE (Left – PCOS; R – hypothalamic hypogonadism)[1]
  - PCOS more frequent in IGE
- AED effects on female sex steroid hormones
  - The incidence of PCOS in people with epilepsy who were treated with valproic acid was 1.95 greater than the incidence in people taking other ASMs[2,3]
  - A 2023 meta-analysis compiled studies that reported PCOS in people exposed to ASMs considered to be mood stabilizers[4] (14/16 studies were in the epilepsy population): valproic acid had the highest likelihood to cause PCOS (OR 6.86, 95% CI 2.92-24.07), while carbamazepine, oxcarbazepine, and lamotrigine also had increased PCOS rates but were not statistically significant
  - Polytherapy may also increase risk of IVF in women with epilepsy[5]

1. Herzog AG. Neurology 1993; 2. Morrell MJ et al. *Ann Neurol* 2008; 3. Xu X et al. *Epilepsy Res* 2011;
4. Guo J et al. *Front Psychiatry* 2023; 5. Sukumaran SC et al. *Neurology* 2010.

Reproductive health and Fertility

- Many studies suggest lower birthrate in WWE – biological or choice?
- USA: state laws allowed forcible sterilization of WWE until 1956[1]
- UK: people with epilepsy were not allowed to marry until 1970[1]
- India: epilepsy was grounds for annulment of marriage until 1999[2]

1. WHO. Epilepsy: social consequences and economic aspects; fact sheet 166. 2001; 2. D'Souza C. Epilepsy and discrimination in India. Neur Asia 2004; 9:53.

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Women with Epilepsy Pregnancy Outcomes and Deliveries
WEPOD

Pennell PB, et al. *JAMA Neurology* 2018.

Prospective cohort observational study – 3 sites:

Healthy control women (n=108)
Women with epilepsy on ASMs (n=89)
- LTG monotherapy (n=39)
- LEV monotherapy (n=25)
- Strong EI-ASMs mono/polytherapy (n=16)

Results:

*WWE and healthy controls seeking pregnancy had **comparable** ovulatory rates, likelihood and time to achieve pregnancy, pregnancy outcomes*

Prospective cohort observational study:

No control group
Women with epilepsy (n=375)
- Most frequently used ASMs: carbamazepine, valproate, phenobarbital, phenytoin

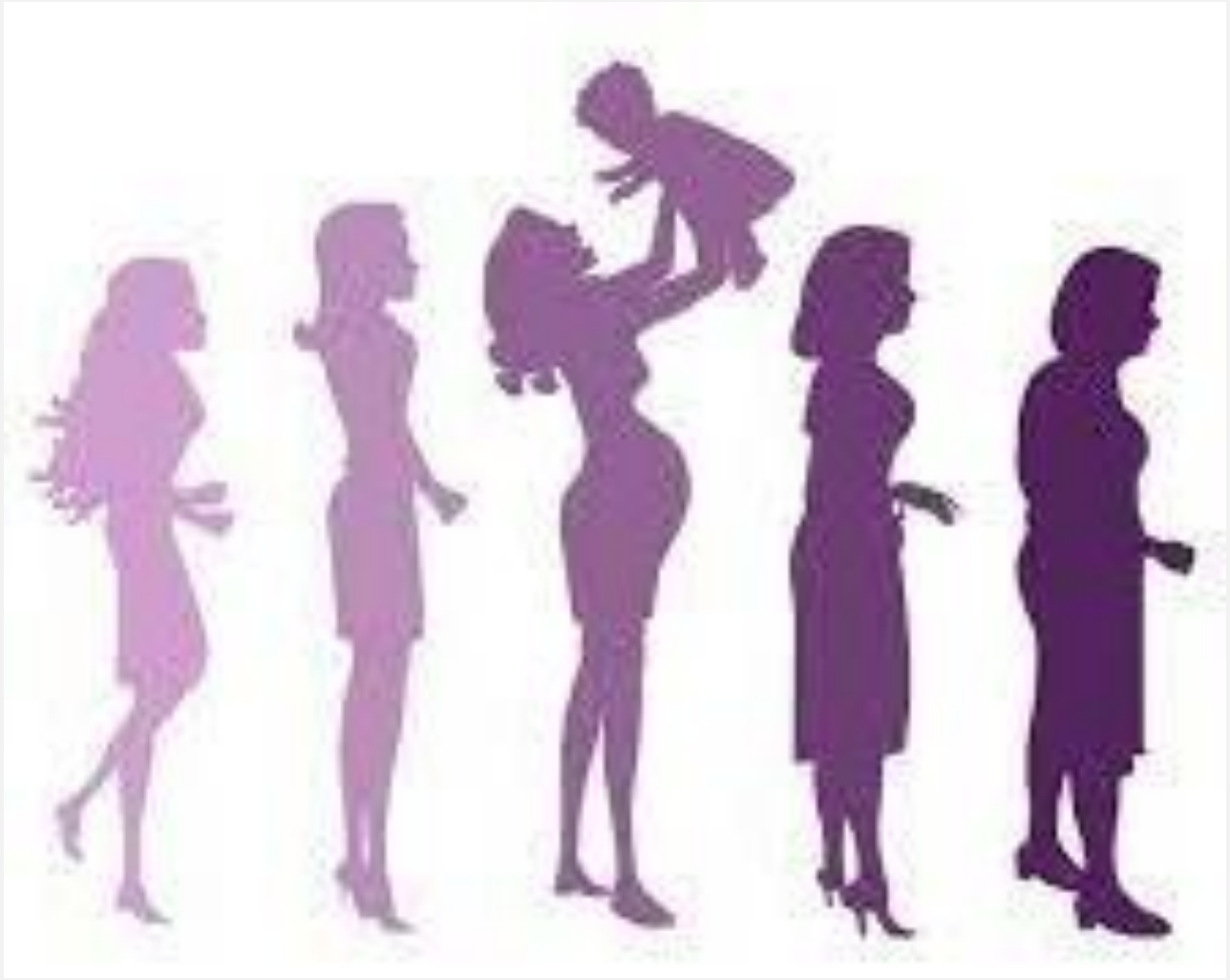
Results:

38.4% WWE had infertillity
Important predictors: polytherapy, PB use, older age and lower education

Kerala Registry of Epilepsy and Pregnancy (1998-2007)

Sukumaran SC, et al. *Neurology* 2010

Personalized Care for Women at Different Biological Stages



Contraception
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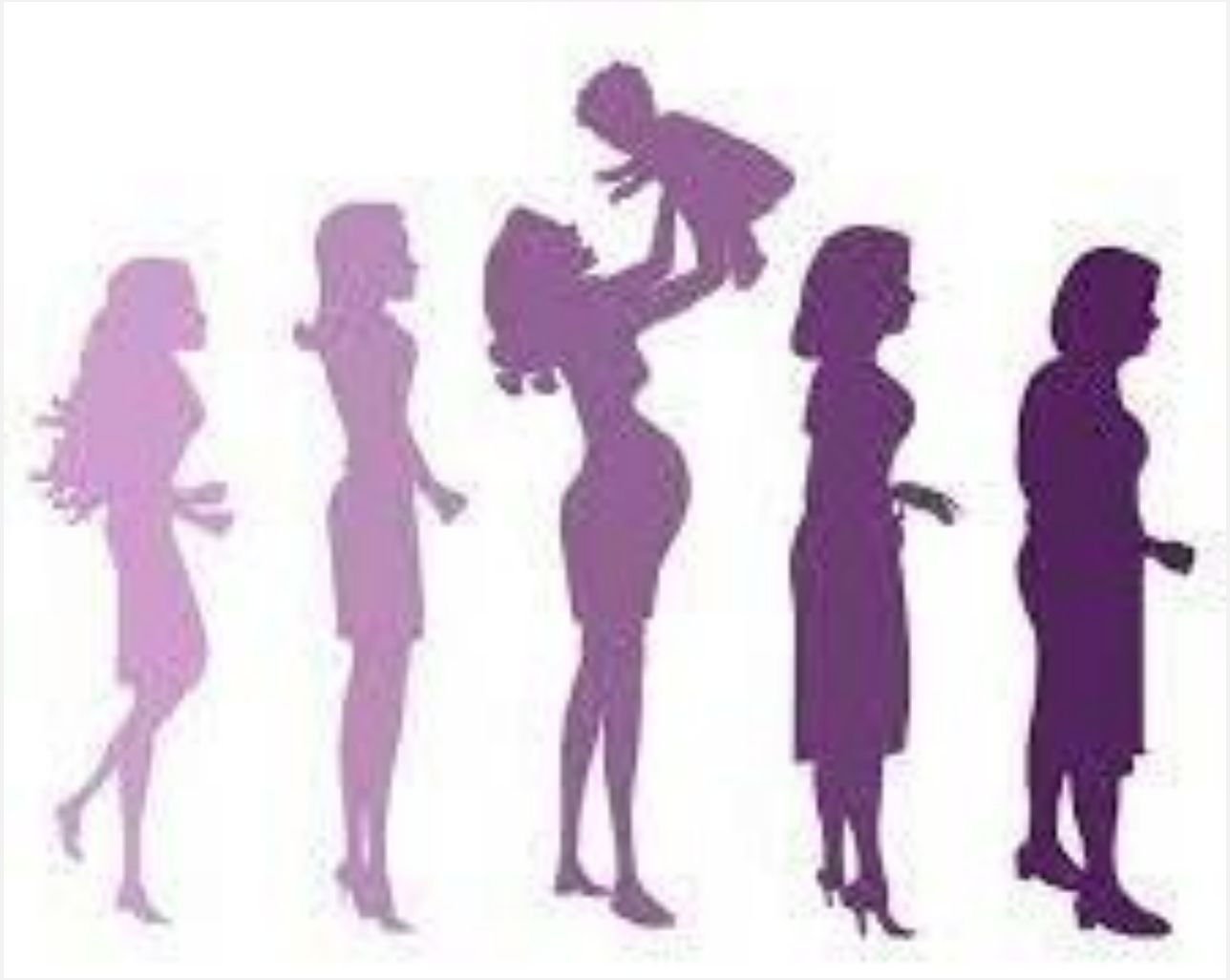
Catamenial Epilepsy

Assisted Reproductive Technology

- One case report detailing two cases of ART in WWE: both experienced seizure worsening, one with a reduction in lamotrigine serum level during IVF[1]
- In a study of Danish health registries from 2006-2017[2], 260 women with epilepsy who underwent ART were included and compared to 42,938 women who underwent ART who did not have epilepsy and found **similar rates** for
  - biochemical pregnancy and clinical pregnancy
  - live births (OR 1.03, 95% CI 0.86-1.25)
  - birth rates between women on ASM monotherapy, polytherapy, or enzyme inducing ASMs
- A case series12 WWE, who underwent 29 embryo transfers, resulting in 16 pregnancies and 10 live births, revealed no increased seizure frequency associated with fertility treatment and subsequent pregnancy
  - 5 WWE were not on ASMs, including three with resolved epilepsy; 7 were on ASMs throughout fertility treatment and pregnancy, with only one on polytherapy.
  - 11/12 remained seizure-free throughout fertility treatment.
  - 1/12 (with drug-resistant epilepsy) continued to have seizures throughout fertility treatment and pregnancy without an exacerbation of seizure frequency

1. Mostacci B et al. *Seizure*. 2018;61:200–2. 2. Larsen MD et al. *Reprod Biomed Online*. 2020;41(6):1015–22. 3. Abdulrazaq AA et al. *Epilepsia*. 2023; 2023;64:e207–e213.

Personalized Care for Women at Different Biological Stages



Contraception
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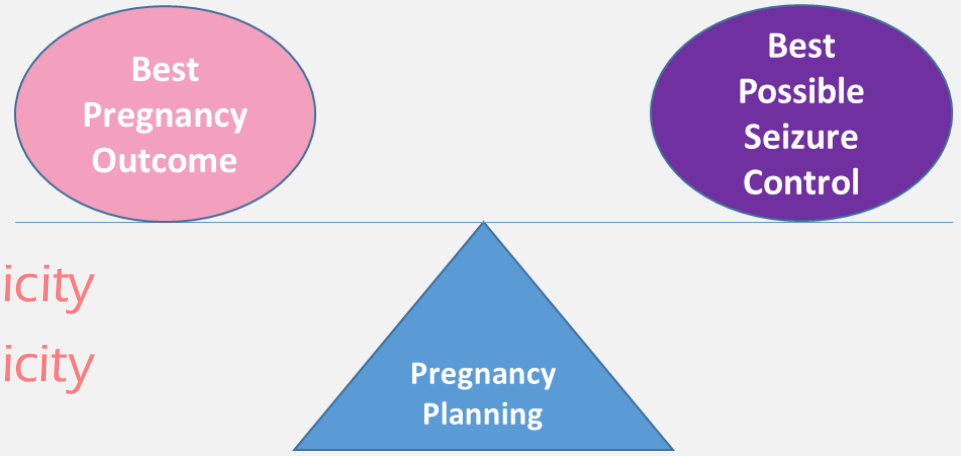
Personalized equation: Benefits versus risks of ASM during pregnancy

Risk of medications

- Structural teratogenicity
- Cognitive teratogenicity
- Neonatal outcomes



Risk of seizures

- On the mother
- On the fetus

Risk of attempting to optimize the ASM regimen

- Seizure control
- Side-effects

ASM, antiseizure medication.
Speaker's opinion.

SPECIAL ARTICLE

Teratogenesis, Perinatal, and Neurodevelopmental Outcomes After In Utero Exposure to Antiseizure Medication

Practice Guideline From the AAN, AES, and SMFM

Alison M. Pack, MD, MPH, Maryam Oskoui, MD, MSc, Shawniqua Williams Roberson, MEng, MD, Diane K. Donley, MD, Jacqueline French, MD, Elizabeth E. Gerard, MD, David Gloss, MD, MPH&TM, Wendy R. Miller, PhD, RN, CCRN, Heidi M. Munger Clary, MD, MPH, Sarah S. Osmundson, MD, MS, Brandy McFadden, Kaitlyn Parratt, MBBS (Hons 1), Page B. Pennell, MD, George Saade, MD, Don B. Smith, MD, Kelly Sullivan, PhD, Sanjeev V. Thomas, MD, DM, Torbjörn Tomson, MD, Mary Dolan O'Brien, MLIS, PMP, Kylie Botchway-Doe, Heather M. Silsbee, MWC, and Mark R. Keezer, MDCM, PhD

Correspondence
American Academy of Neurology
guidelines@aan.com

Neurology® 2024;102:e209279. doi:10.1212/WNL.0000000000209279

AAN - General Recommendations

Recommendation 1 Statements

1(A) Clinicians should engage in joint decision-making with PWECP, taking individual preferences into account when selecting ASMs and monitoring their dosing (Level B).

1(B) When treating PWECP, clinicians should recommend ASMs and doses that optimize both seizure control and fetal outcomes should pregnancy occur, at the earliest possible opportunity preconceptionally (e.g., at the time of starting an ASM in a person post-menarche) (Level B).

Preconception PLANNING

1. Ensure **adequate** contraception **(check interactions with ASMs)**
2. Recommend folic acid **(1mg daily)**; consider prenatal vitamin supplementation
3. **Clarify the** diagnosis: non-epileptic vs epileptic; focal vs generalized; known etiology?; surgical?
4. Optimize ASM regimen for seizure control and pregnancy outcome:
    1. Consider switching to an ASMs with a better pregnancy outcome profile
    2. Monotherapy preferred to polytherapy
    3. Reduce to minimal effective dose
    4. If polytherapy is necessary, some ASMs are preferable (LTG, LEV) while some should be avoided (VPA, PB, TPM)
5. Determine **individualized therapeutic** ASM baseline concentration (ASM concentration on the minimal effective dose)

ASM, antiseizure medication; LEV, levetiracetam; LTG, lamotrigine; PB, phenobarbital; TPM, topiramate; VPA, valproic acid.
Voinescu PE and Pennell PB. *Semin Neurol*. 2017;37:611–623. Voinescu, P.E., Meador, K.J. *Curr Obstet Gynecol Rep*. 2022

AAN – Folic Acid

Recommendation 6 Statements

6A. Clinicians should prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to decrease the risk of NTDs in the offspring (Level B).

6B. Clinicians must prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to possibly improve neurodevelopmental outcomes such as ASD and global IQ in the offspring (Level A).

6C. Clinicians should counsel PWECP treated with an ASM that adherence to recommended folic acid supplementation preconceptionally and during pregnancy is important to minimize the risk of MCMs and poor neurodevelopmental outcomes (Level B).

The effects of folic acid on structural teratogenicity

- Reduced risks of MCMs in the general population

Neural tube defects[1,2,3]

Congenital heart defects[4,5]

Oral clefts[6]

MCMs, major congenital malformations

1. Czeizel AE, Dudás I. *N Engl J Med.* 1992 Dec 24;327(26):1832-5
2. Werler MM et al. JAMA. 1993;269:1257-1261.
3. MRC Vitamin Study Research Group. Lancet. 1991 Jul 20;338(8760):131-7. PMID: 1677062.
4. Shaw GM et al. Am J Med Genet. 1995;59(4):536–45.
5. Czeizel AE. *Am J Med Genet*. 1996;62(2):179-183.
6. Badovinac RL et al. Birth Defects Res A Clin Mol Teratol. 2007 Jan;79(1):8-15.

The effects of folic acid on neurodevelopmental teratogenicity

- Folic acid supplementation ***for women with epilepsy (and not only)*** was associated with their children's:
  - 5-point higher IQ[1]
  - Reduced risks for language delay[2]
  - Reduced risk of autism[3,4,5]

IQ, intelligence quotient; CI, confidence interval.

1. Meador et al. *The Lancet Neurology.* 2013;12(3):244–52.
2. Husebye ESN et al. *Neurology*. 2018;91(9):e811–21.
3. Bjørk M et al. *JAMA Neurology.* 2018 Feb 1;75(2):160-168.
4. Wang M, Li K, Zhao D, Li L. *Mol Autism.* 2017 Oct 2;8:51.
5. Gao Y et al. PLoS One. 2016 Nov 22;11(11):e0165626.

Negative effects of folic acid in pregnancy

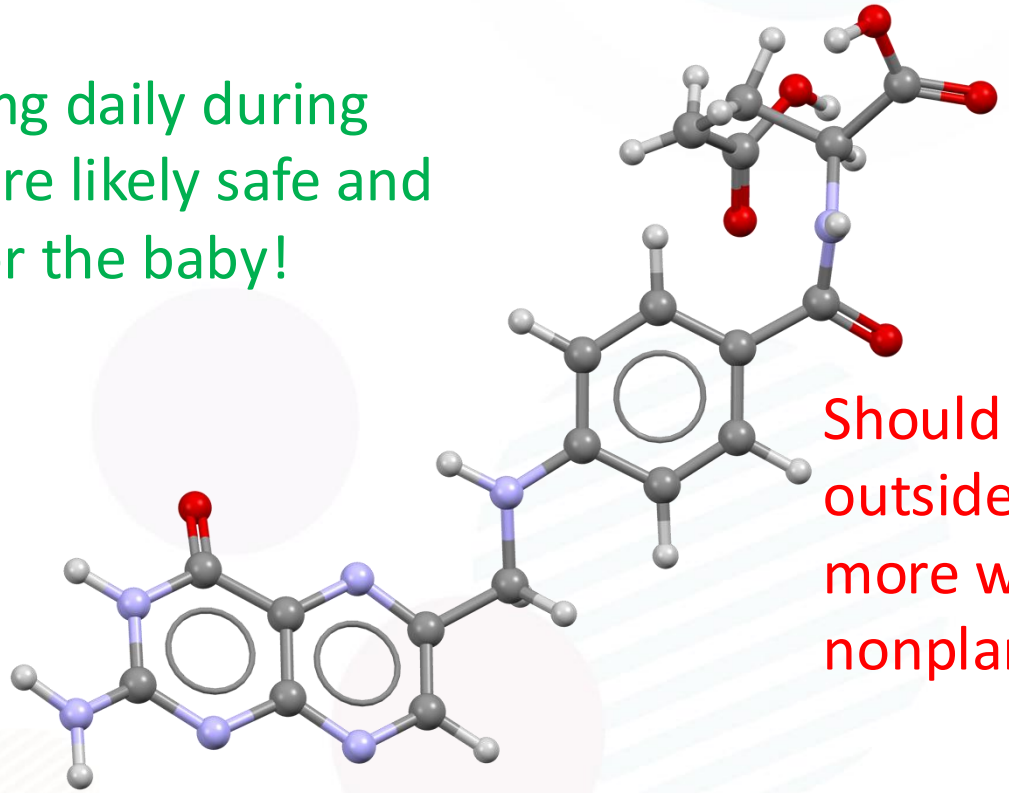
- Possible increased risk in the rate of pediatric cancer in the offsprings of mothers' with epilepsy[1]
- Possible increase in the rate of non-Hodgkin lymphoma in mothers on high dose folic acid[2]
- Negative neurodevelopmental outcomes?[3,4]

ASM, antiseizure medication. MONEAD, Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs

1. Vegrim HM et al. *JAMA Neurol*. 2022 Nov 1;79(11):1130-1138.
2. Vegrim HM et al. *Epilepsia*. 2024 Nov 14. doi: 10.1111/epi.18146. Epub ahead of print.
3. Valera-Gran D et al. *JAMA pediatrics*. 2014 Nov 1;168(11):e142611-.
4. Valera-Gran D et al. *The American journal of clinical nutrition.* 2017 Mar 1;106(3):878-87.

To take or not to take a "high" dose folic acid during the reproductive years? What is low and what is high?

Doses of 3 mg daily during pregnancy are likely safe and beneficial for the baby!



Should we consider lower doses outside pregnancy? And increase to more when planning? What about nonplanned pregnancies?

A study to determine optimal dose for maximal benefits and minimal negative effects is necessary.

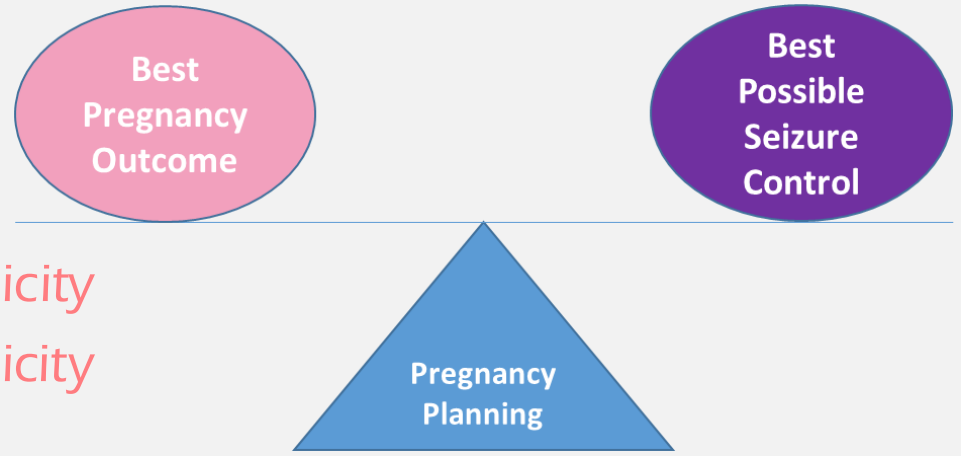
PREGNANCY

- Structural and cognitive teratogenicity
- Neonatal/Obstetrical outcomes
- Pharmacokinetic considerations

Antiseizure medications and pregnancy

Education regarding the risk of ASMs and risk of seizures is important

Personalized equation: Benefits versus risks of ASM during pregnancy



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Risk of seizures

- On the mother
- On the fetus

Risk of attempting to optimize the ASM regimen

- Seizure control
- Side-effects

ASM, antiseizure medication.
Speaker's opinion.

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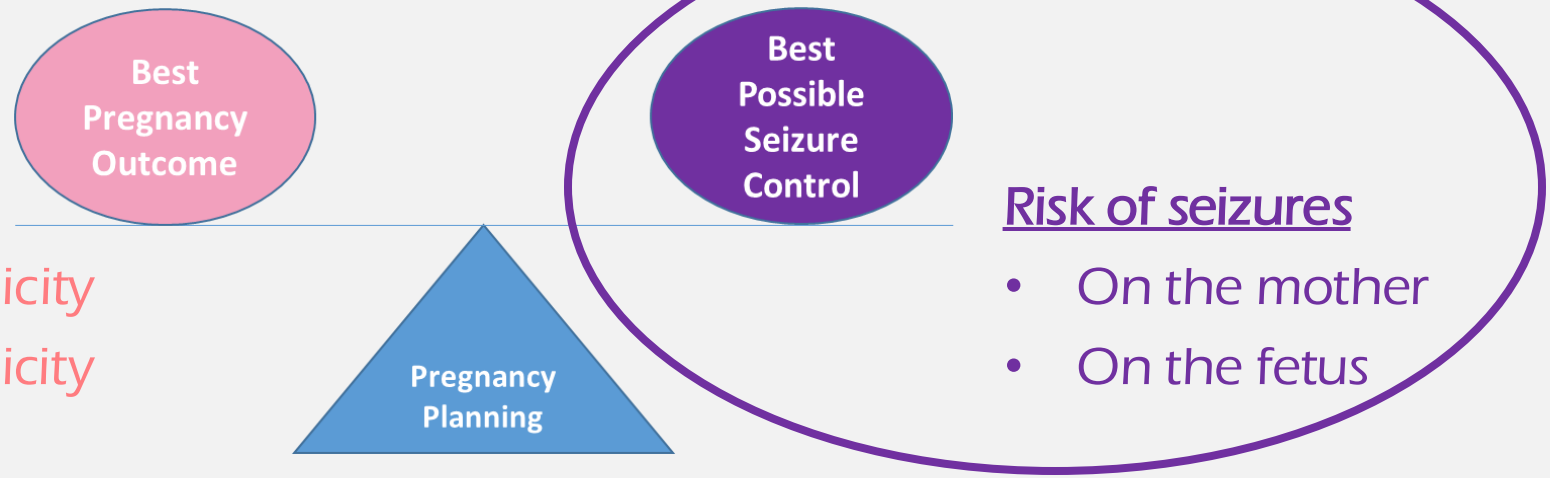

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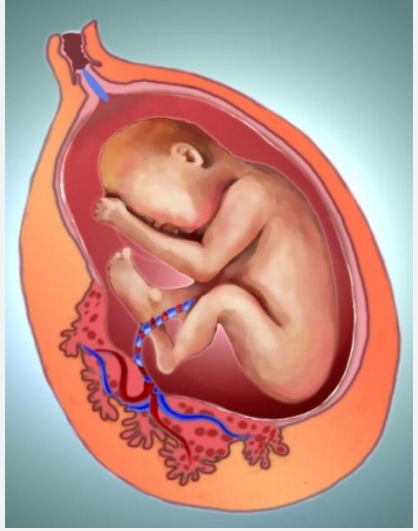
Risk of Seizures



Generalized Tonic-Clonic Convulsions

- Maternal & fetal hypoxia & acidosis, fetal brady
- Miscarriage & stillbirths
- Developmental delay (≥5 GTCC in pregnancy)

All seizures:

- Increased OR for LBW, SGA, preterm delivery **(1.3-1.6 fold)**

Status epilepticus

- 30% maternal mortality; 50% infant mortality

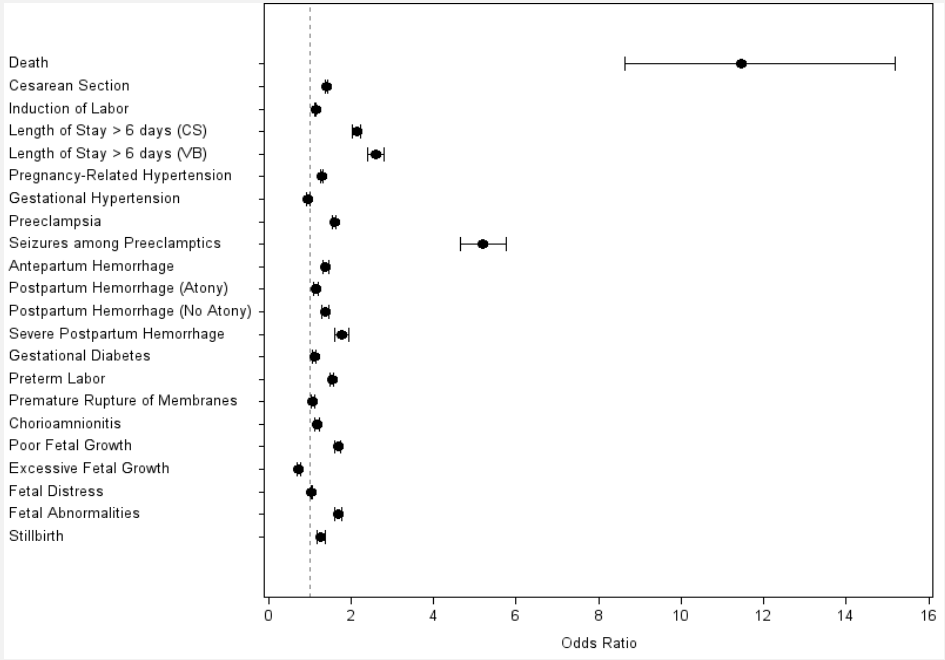
Maternal Risks

- Death rate during pregnancy in WWE 10-fold higher (SUDEP)
- 11.5 OR [95% CI, 8.64-15.19]), of death during delivery hospitalization

Teramo K, et al. *J Perinat Med.* 1979;7(1):3-6; Vinten J, et al. *Neurology* 2005;64(6):949-54; Chen YH, et al. *Arch Neurol* 2009;66(8):979-84; Macdonald SC, et al. JAMA Neurol 2015; Fu Y, Shi F, Sha L, et al.*Journal of Neurology, Neurosurgery & Psychiatry* 2025.

Maternal Outcomes

Nationwide Inpatient Sample - Retrospective Study



MacDonald SC et al. *JAMA Neurology.* 2015

MONEAD Study

Key Points

- Unlabored cesarean rates higher among women with epilepsy.
- Provider preference may influence delivery mode among women with epilepsy.
- Type and amount of antiepileptic drug was not associated with mode of delivery.

McElrath TF et al. *Am J Perinatol.* 2022

- ScanAED: WWE had a 23% higher risk of life-threatening complications and approximately 4-fold higher risk of death and in pregnancy and the postpartum period

  Razaz N et al. *JAMA Neurology.* 2024

- UK and Ireland: 2nd most common indirect cause of maternal death; SUDEP may be the leading cause (10 times higher risk of sudden death during pregnancy)

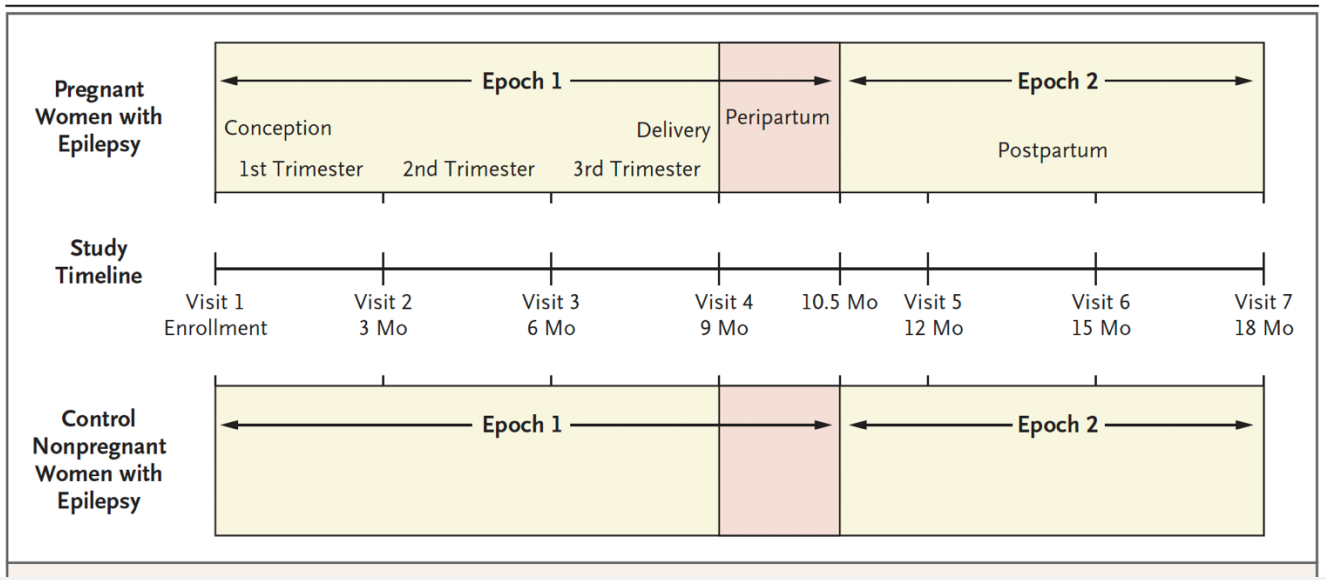
  Knight M et al. MBRRACE-UK
  Edey S et al. *Epilepsia* 2014

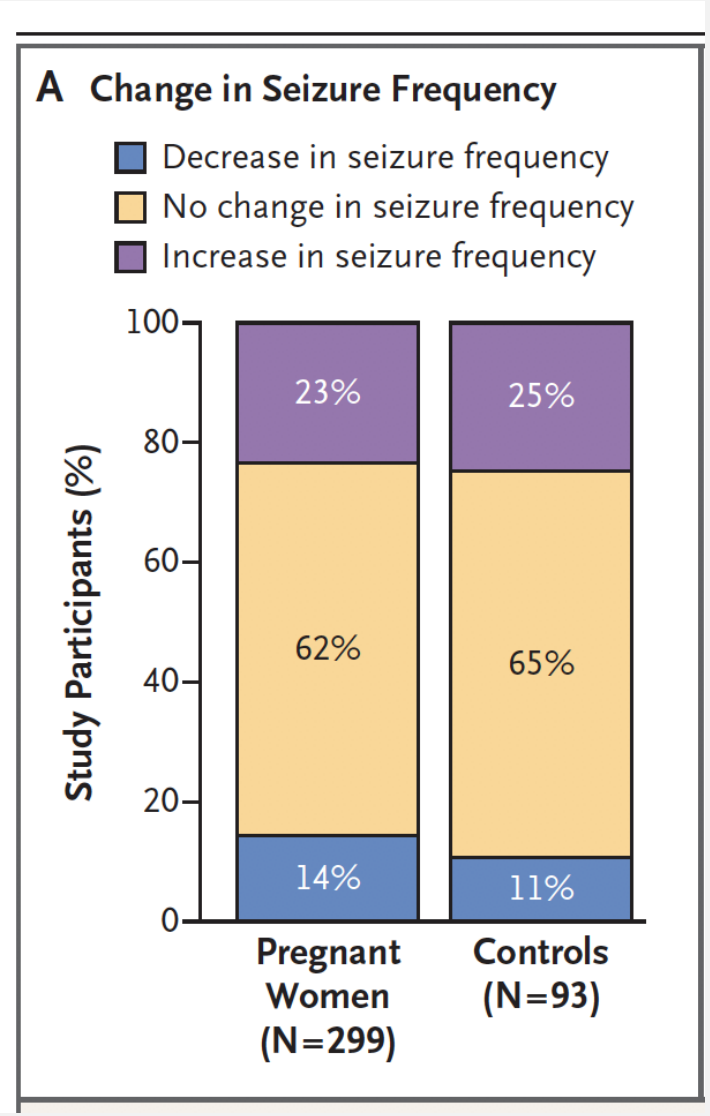
- Meta-analysis: WWE have a 5 times higher odds of maternal death

  Mazzone PP et al. *JAMA Neurol.* 2023

Change in Frequency of Seizures that Impair Awareness in Pregnant Women vs. Control Women with Epilepsy

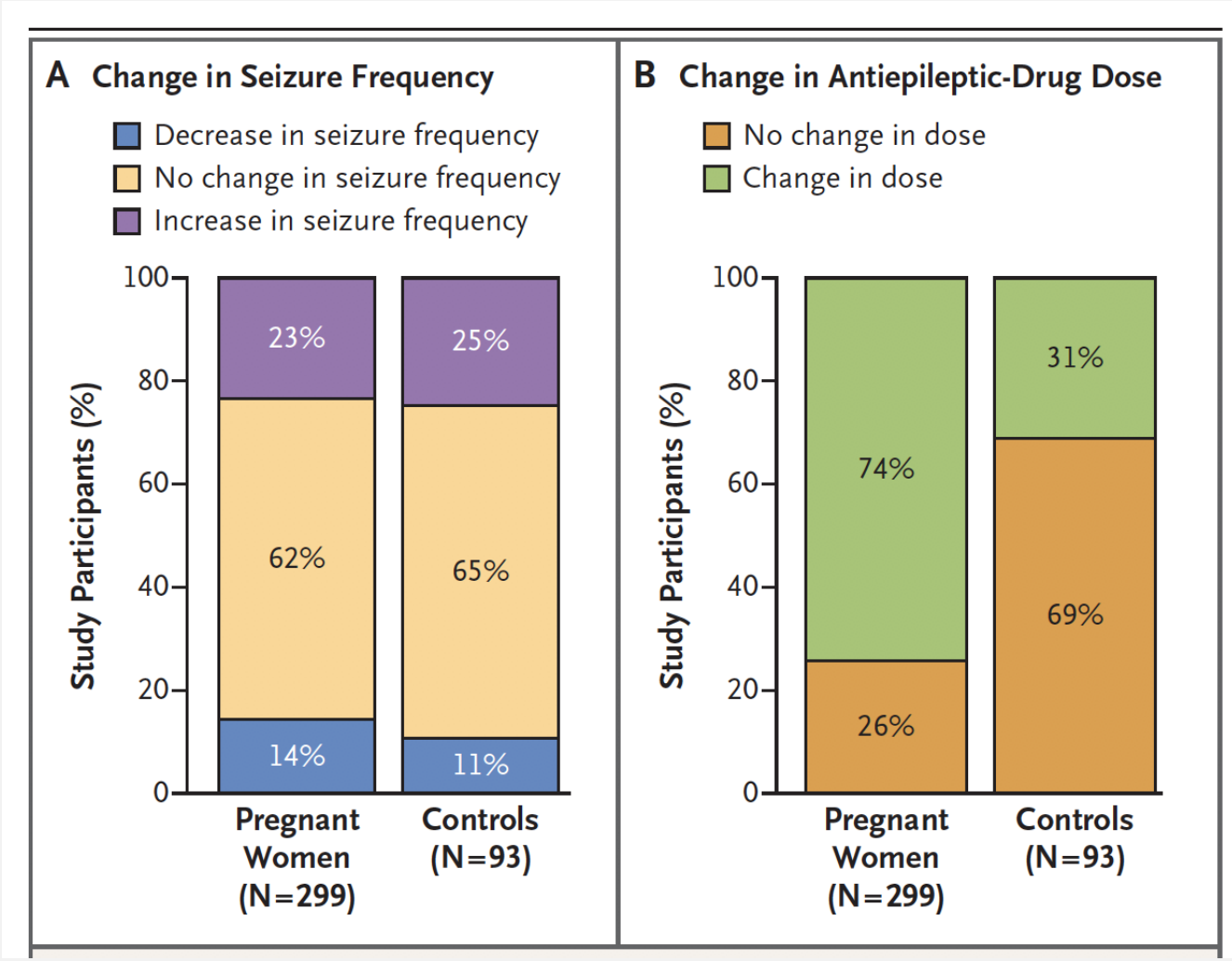
MONEAD Study Design for Seizure Outcomes





Pennell PB et al. Changes in Seizure Frequency and Antiepileptic Therapy during Pregnancy. *N Engl J Med.* 2020 Dec 24;383(26):2547-2556.

Change in Frequency of Seizures that Impair Awareness in Pregnant Women vs. Control Women with Epilepsy



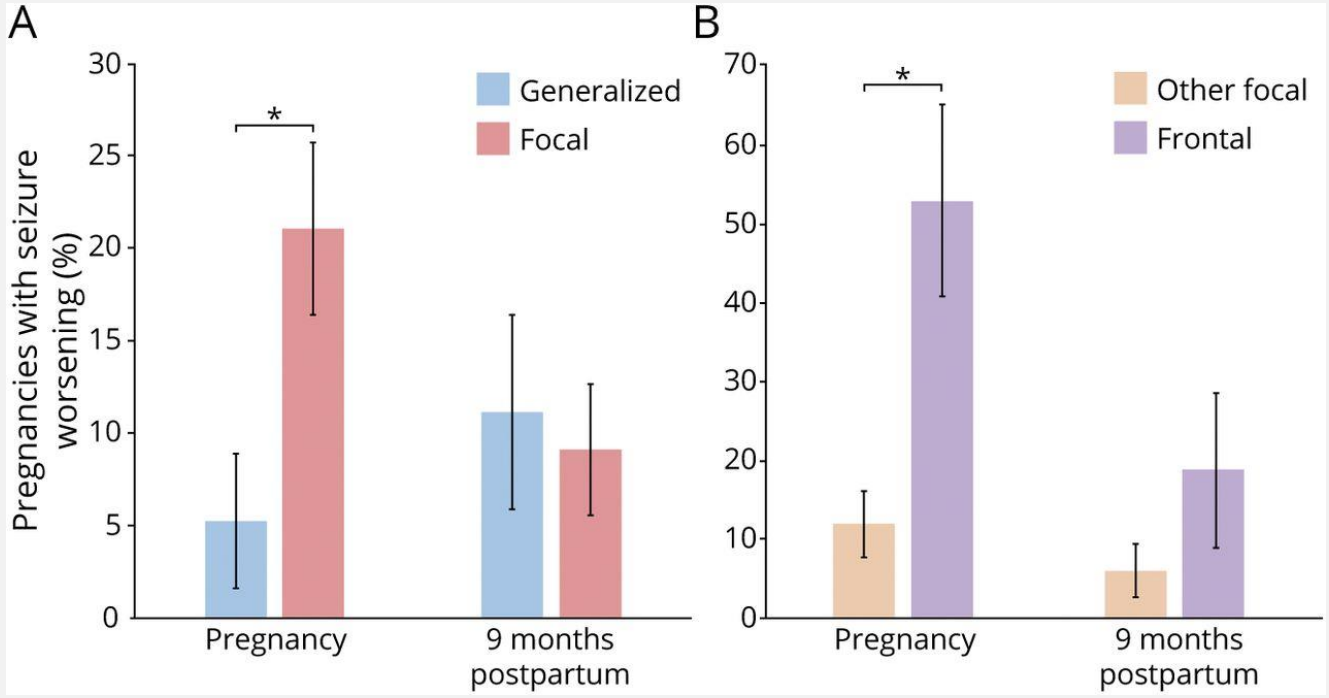
Pennell PB, French JA, May RC, et al. N Engl J Med. 2020 Dec 24;383(26):2547-2556.

Risk Factors for worsening of seizures with impaired awareness during pregnancy and peripartum

- Evaluated in 23% of PWWE with increased seizures with impaired awareness (incl. GTCS)
- No differences in seizure types, ASM regimen or type
- Sole risk factor was seizure freedom in 9 months prior to conception:
  - Adjusted OR = 0.26, 95% CI [0.14, 0.46], p<0.001).

Pennell PB, French JA, May RC, et al.. Changes in Seizure Frequency and Antiepileptic Therapy during Pregnancy. N Engl J Med. 2020 Dec 24;383(26):2547-2556.

Variations in Seizure Frequency during Pregnancy and Postpartum by Epilepsy Type



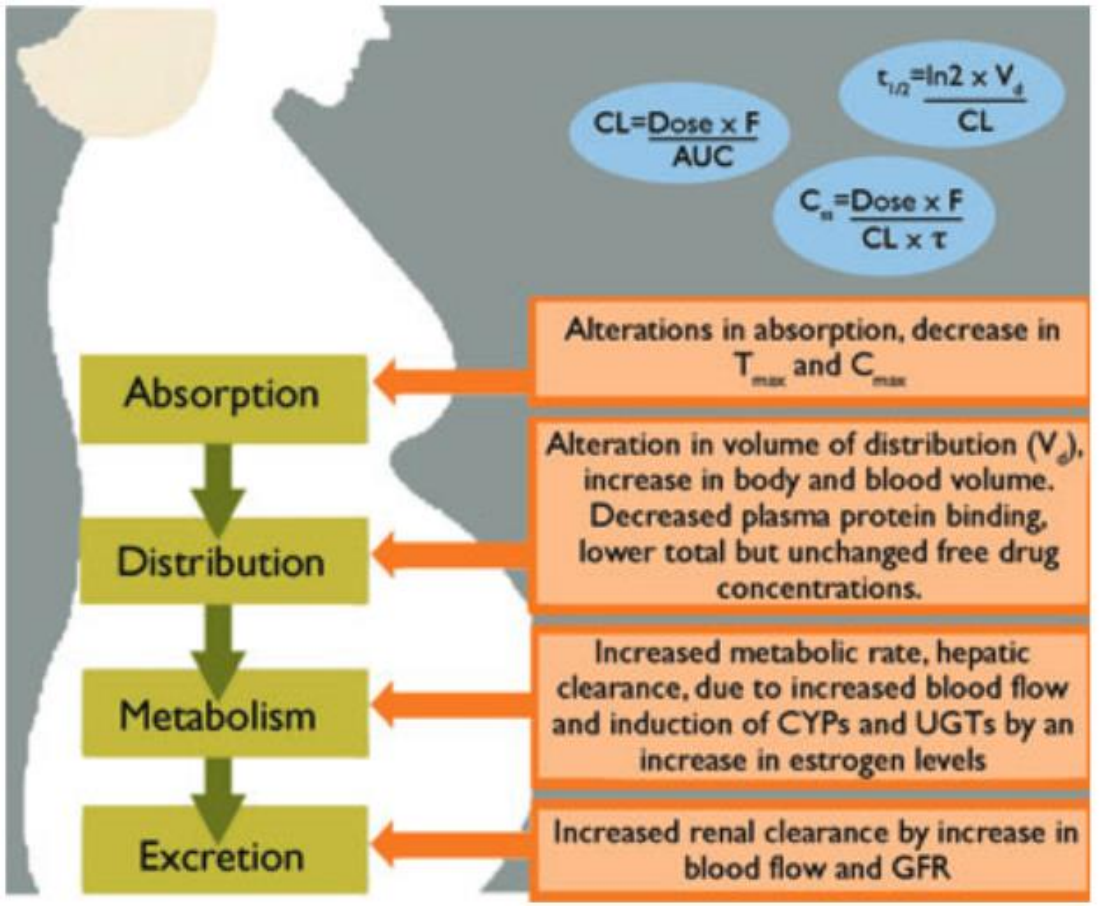
- 99 patients contributing 114 pregnancies
- **Increased** seizure frequency during pregnancies of women with :
  - ❖ **focal** vs generalized epilepsy: 21.1% vs 5.3%, **OR 4.70**; 95% CI (1.00, 22.00); p = 0.0497
  - ❖ **frontal** lobe vs other focal epilepsy: **OR 8.00**; 95 % CI (2.19, 29.21); p = 0.0017
  - ❖ **polytherapy** vs monotherapy: **OR = 8.36**, 95% CI = (2.07, 33.84), p = 0.0029 - regardless of the medication or epilepsy type
  - ❖ **Lack** vs presence of **preconception seizure freedom**: **OR = 6.418**; p = 0.0076

Voinescu PE et al. *Neurology* Feb 2022, 98 (8) e802-e807

PREGNANCY - POSTPARTUM

- Pharmacokinetic considerations

Pharmacokinetic changes in drug disposition during pregnancy



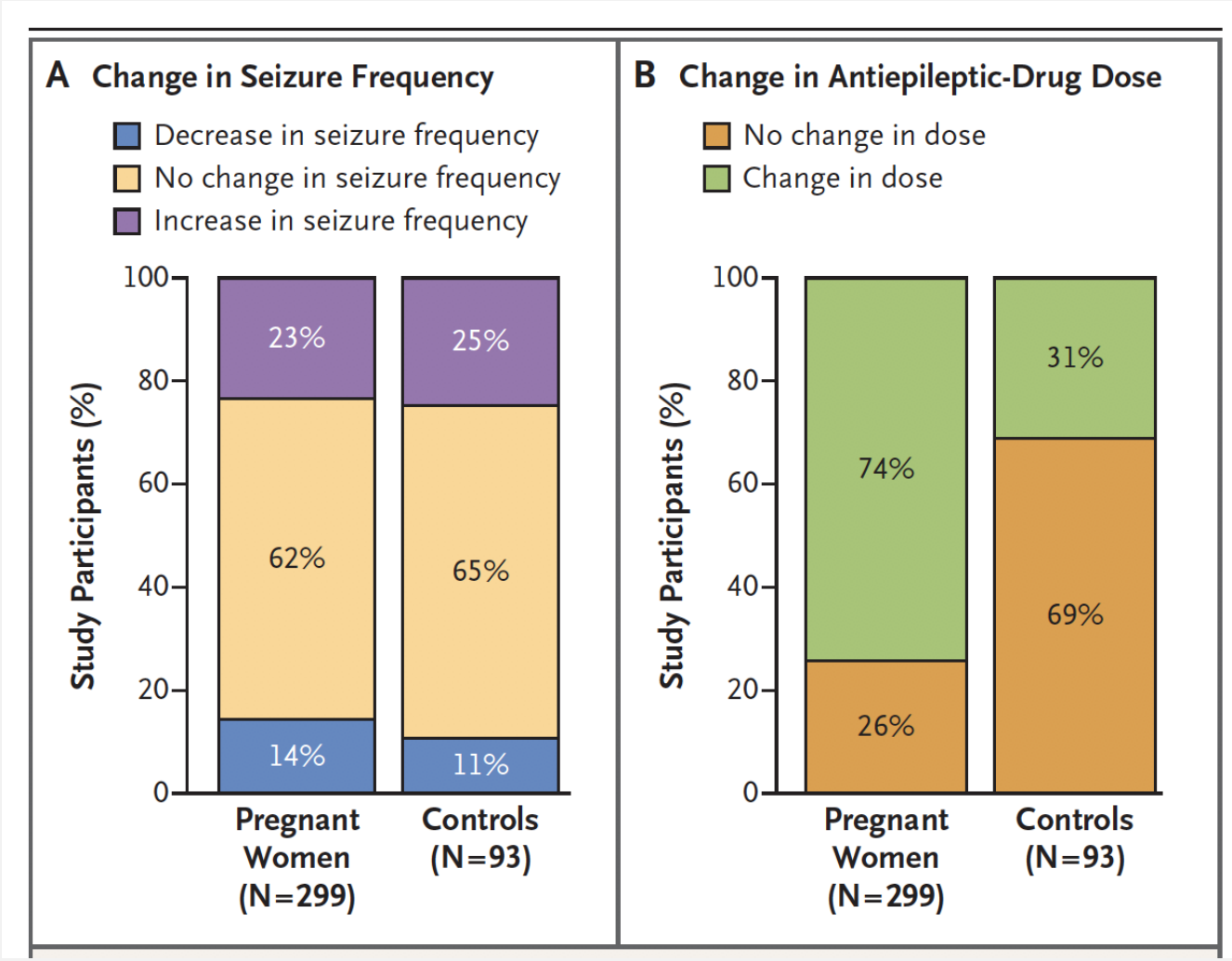
Tomson et al. *Epilepsia* 2013 ILAE

Direction of pharmacokinetic changes for antiseizure medications during pregnancy

ASM	Concentration	Clearance	Timing of Peak Clearance
Carbamazepine	No change	No change	N/A
Carbamazepine-Epoxide	No change	No change	N/A
Lacosamide	Decrease	Increase	N/A
Levetiracetam	Decrease	Increase	1st trimester
Lamotrigine	Decrease	Increase	3rd trimester
Phenytoin	Decrease	Increase	3rd trimester
Phenobarbital	Decrease	Increase	N/A
Oxcarbazepine	Decrease	Increase	2nd/3rd trimester
Topiramate	Decrease	Increase	2nd/3rd trimester
Valproate	Decrease	No change	N/A
Zonisamide	Decrease	Increase	3rd trimester

Adapted from Lemley RL and Voinescu PE. Queenan's Management of High-Risk Pregnancy: An Evidence-Based Approach, 7th edition

Change in Frequency of Seizures that Impair Awareness in Pregnant Women vs. Control Women with Epilepsy



Pennell PB, French JA, May RC, et al. N Engl J Med. 2020 Dec 24;383(26):2547-2556.

Summary of pharmacokinetic changes

- The magnitude and time course of pregnancy-related pharmacokinetic changes vary for different ASM[1-4]
- Dose adjustments are necessary to maintain a pre-conception target concentration[5]
- **A decrease by more than 35% of the preconception baseline is associated with a significant increase in seizure frequency**[1,3]
- Extended-release formulations and twice (or more times) per day dosing are preferred to minimize ASM level fluctuations

The Obstetrician is our partner in keeping seizures under control during pregnancy by helping with monthly blood drawns to check antiepileptic drug serum concentration (level)

1. Voinescu PE et al. Neurology 2018;91:e1228-e1236; 2. Johnson et al. Epilep Behav 2014;33:49–53; 3. Pennell et al. Neurology 2007;70(22 Pt 2):2130–6. 4. Pennell PB, et al. MONEAD Study Group. JAMA Neurol. 2022;79(4):370-379. 5. Pennell PB, et al. MONEAD Study Group. NEJM. 2020; 383(26):2547-2556

AAN - General Recommendations

Recommendation 2 Statements

2A. Clinicians must minimize the occurrence of convulsive seizures (generalized tonic-clonic seizures and focal-to-bilateral tonic-clonic seizures) in PWECP during pregnancy to minimize potential risks to the birth parent (e.g., seizure-related mortality) and to the fetus (Level A).

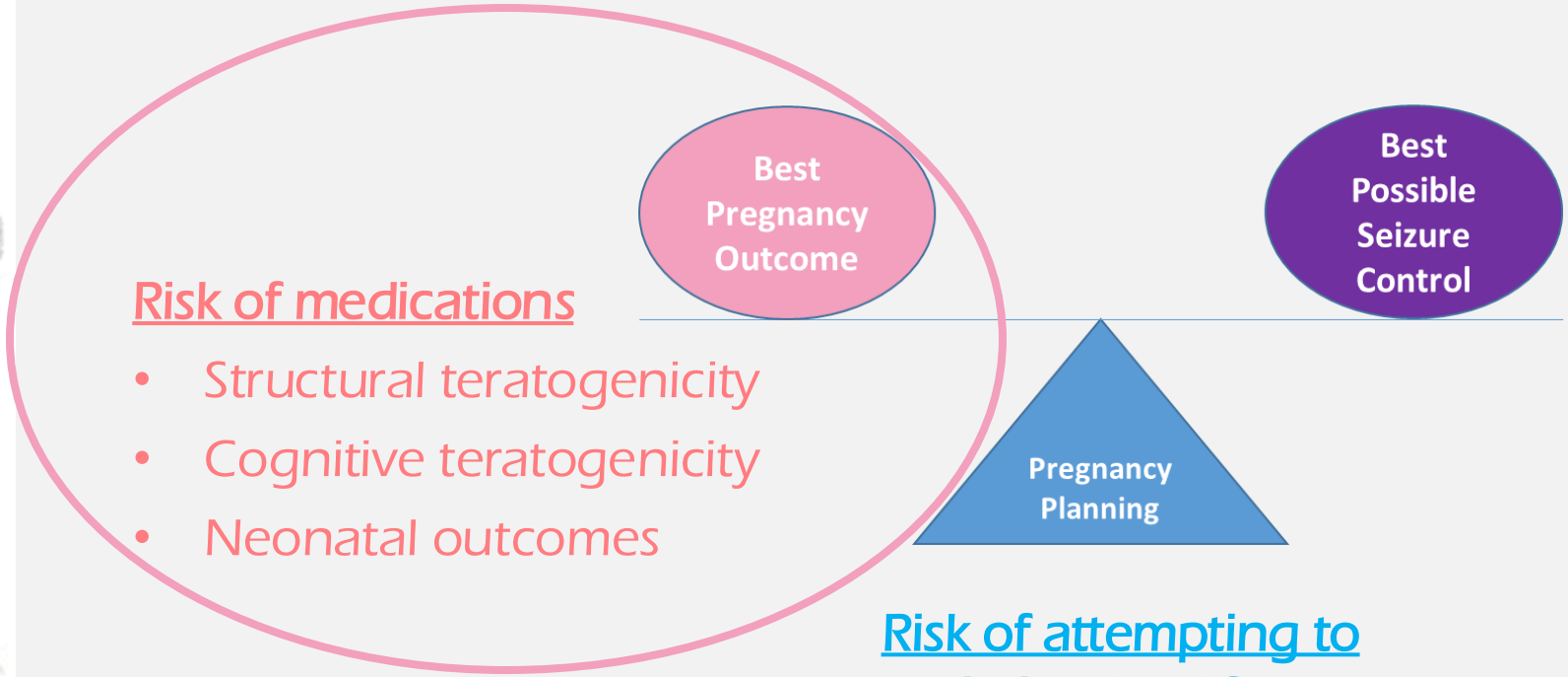
2B. Once a PWECP is already pregnant, clinicians should exercise caution in attempting to remove or replace an ASM that is effective in controlling generalized tonic-clonic or focal-to-bilateral tonic-clonic seizures, even if it is not an optimal choice with regards to the risk to the fetus (e.g., valproic acid) (Level B).

2C. Clinicians should monitor ASM levels in PWECP throughout pregnancy as guided by individual ASM pharmacokinetics and patient clinical presentation (Level B).

2D. Clinicians should adjust the dose of ASMs at their clinical discretion during the pregnancy in response to (1) decreasing serum ASM levels or (2) worsening seizure control (observed or anticipated based on the clinician's judgment and known pharmacokinetics of ASMs in the pregnant state) (Level B).

2E. Clinicians treating PWECP using acetazolamide, eslicarbazepine, ethosuximide, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, or vigabatrin should counsel their patients that there are limited data on pregnancy-related outcomes for these drugs (Level B).

Personalized equation: Benefits versus risks of ASM during pregnancy



Risk of medications

- Structural teratogenicity
- Cognitive teratogenicity
- Neonatal outcomes

Risk of seizures

- On the mother
- On the fetus

Risk of attempting to optimize the ASM regimen

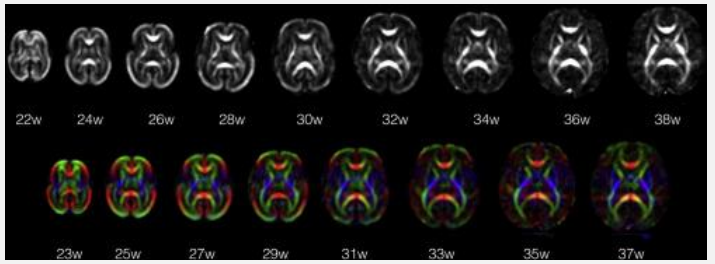
- Seizure control
- Side-effects

ASM, antiseizure medication.
Speaker's opinion.

PREGNANCY

Structural Teratogenicity

Neurodevelopmental Effects



Timing of certain MCMs

Tissues	Malformations	Postconceptional age
CNS	Neural tube defect	28 d
Heart	Ventricular septal defect	42 d
Face	Cleft lip	36 d
	Cleft maxillary palate	47–70 d
Genitourinary	Hypospadias	84 d

Structural teratogenicity may be irreversible by the time the pregnant woman is seen in clinic!

CNS, central nervous system; MCMs, major congenital malformations.
http://www.columbia.edu/itc/hs/medical/humandev/2004/Chpt23-Teratogens.pdf

Summary of ASM structural & neurodevelopmental effects

- Structural teratogenicity may be irreversible by the time the pregnant woman is seen in clinic – **Planned pregnancy is key!**
- Rate of MCMs with exposure to ASM monotherapy - green with no noticeable impact and red with negative impact on neurodevelopment
  - Low: **LTG, LEV,** OXC, ZNS, (LCM, GBP)
  - Medium: **CBZ, PHT** (CLZ)
  - High: **TPM, PB, VPA**
- Rate of SGA – higher for TPM, PB >ZNS
- Optimize ASM regimen for seizure control and pregnancy outcome:
  - Consider switching to an ASM with a better pregnancy outcome profile
  - Monotherapy preferred to polytherapy
  - Reduce to minimal effective dose
  - If polytherapy is necessary, some ASMs are preferable (LTG, LEV) while some should be avoided (VPA, TPM)

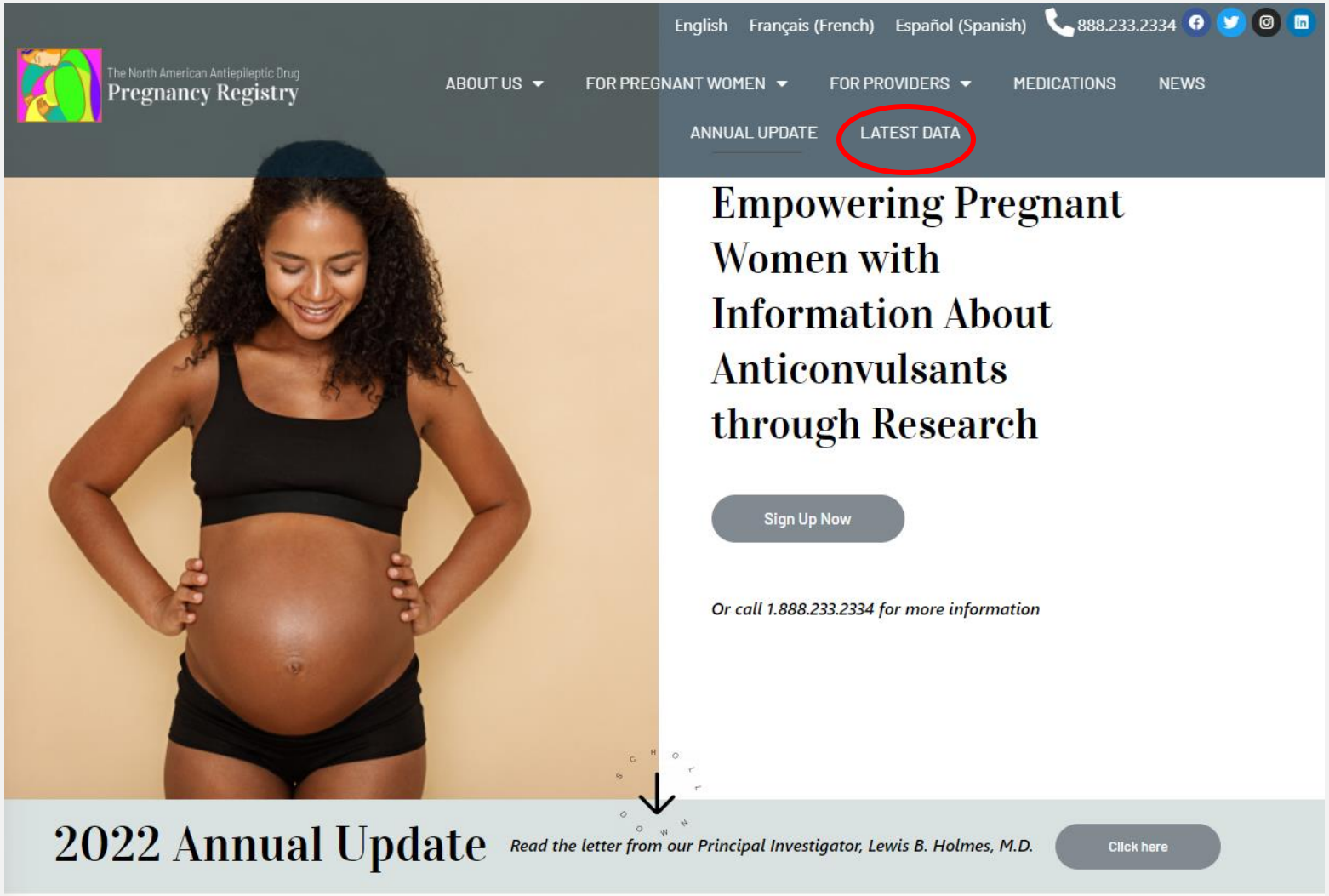
ASM, antiseizure medication; CBZ, carbamazepine; CLZ, clonazepam; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; MCM, major congenital malformations; OXC, oxcarbazepine; SGA, small gestational age; PB, phenobarbital; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.

Voinescu PE and Pennell PB. Semin Neurol. 2017;37:611–623.

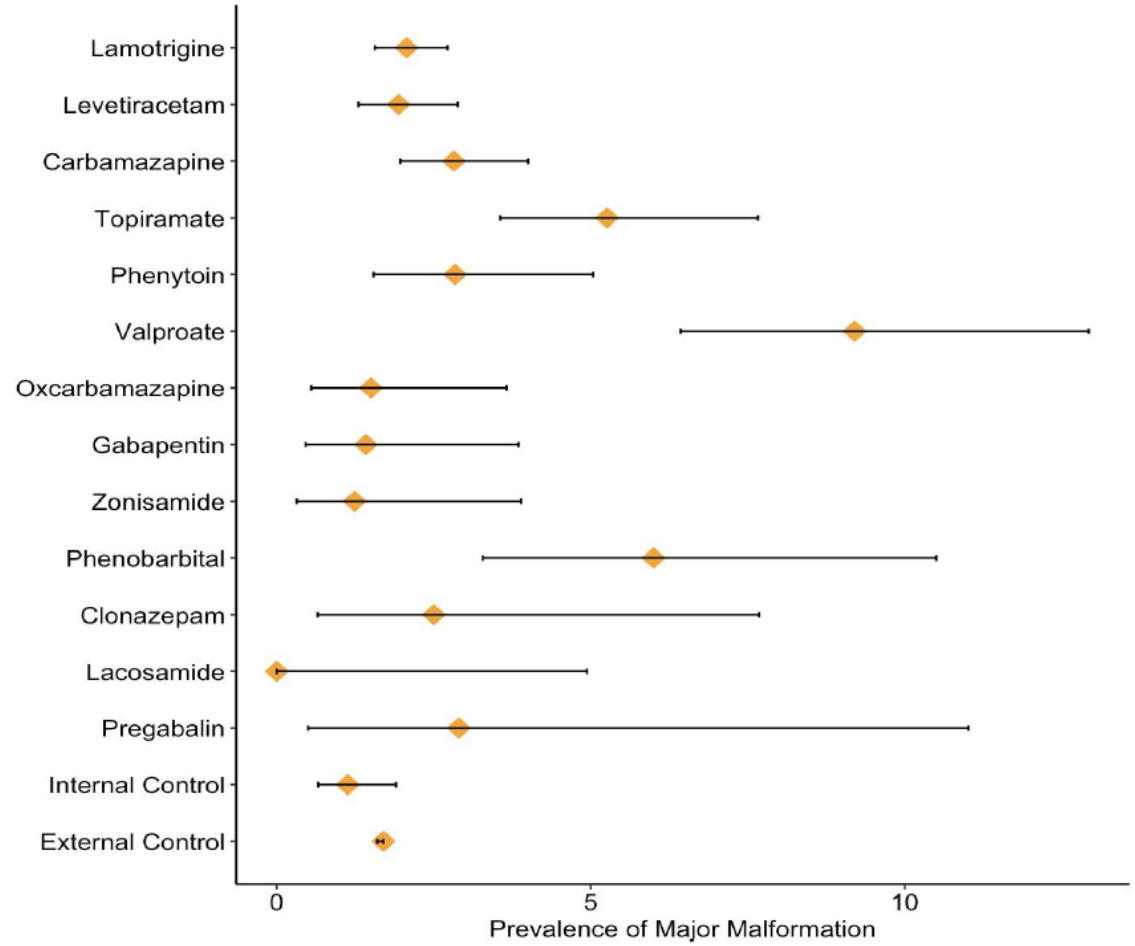
PREGNANCY

Structural Teratogenicity

NAAPR : www.aedpregnancyregistry.org



Risk of malformations for specific AED in monotherapy 1st trimester and the control groups through 2023



	%	N	95% CI
Lamotrigine	2.07	2514	(1.56, 2.72)
Levetiracetam	1.94	1337	(1.3, 2.88)
Carbamazapine	2.82	1135	(1.97, 4)
Topiramate	5.26	513	(3.56, 7.66)
Phenytoin	2.84	423	(1.54, 5.04)
Valproate	9.2	337	(6.43, 12.93)
Oxcarbamazapine	1.5	334	(0.55, 3.66)
Gabapentin	1.42	281	(0.46, 3.85)
Zonisamide	1.24	241	(0.32, 3.89)
Phenobarbital	6	200	(3.28, 10.5)
Clonazepam	2.5	120	(0.65, 7.68)
Lacosamide	0	93	(0, 4.94)
Pregabalin	2.9	69	(0.5, 11.01)
Internal Control	1.13	1330	(0.66, 1.9)
External Control	1.7	289365	(1.6, 1.7)

ASM, antiseizure medication; NAAPR, North American Antiepileptic Drug Pregnancy Registry; MCM, major congenital malformation.

Comparative Safety of ASMs During Pregnancy

Table 2. Prevalence of Major Congenital Malformations (MCMs) in Offspring Exposed Prenatally to Monotherapy With 1 of 8 Different Antiseizure Medications (ASMs)[a]

ASM treatment (dose range, mg/d)	No. Exposed pregnancies	No. Pregnancies with MCMs	Prevalence of MCMs (95% CI), %	Dose-dependency *P* value
Carbamazepine (25-2400)	2255	121	5.4 (4.5-6.4)	NA
Lamotrigine (5-1300)	3584	110	3.1 (2.5-3.7)	
Levetiracetam (80-5000)	1325	33	2.5 (1.8-3.5)	
Oxcarbazepine (75-4500)	443	13	2.9 (1.7-5.0)	
Phenobarbital (15-300)	338	21	6.2 (4.1-9.3)	
Phenytoin (30-730)	142	9	6.3 (3.4-11.6)	
Topiramate (25-600)	204	10	4.9 (2.7-8.8)	
Valproate (100-3000)	1549	153	9.9 (8.5-11.5)	
Phenobarbital (≤60)	76	2	2.6 (0.3-9.2)	.047
Phenobarbital (>60-≤130)	197	12	6.1 (3.2-10.4)	
Phenobarbital (>130)	65	7	10.8 (4.4-20.9)	
Carbamazepine (≤700)	1506	70	4.6 (3.6-5.8)	.008
Carbamazepine (>700 -≤1000)	541	32	5.9 (4.1-8.2)	
Carbamazepine (>1000)	208	19	9.1 (5.6-13.9)	
Valproate (≤650)	715	43	6.0 (4.4-8.0)	<.001
Valproate (>650-≤1450)	711	79	11.1 (8.9-13.6)	
Valproate (>1450)	123	31	25.2 (17.8-33.8)	

Battino et al, *JAMA Neurology.* 2024.
EURAP, European Registry of Antiepileptic drugs and Pregnancy

AAN – ASMs: MCMs

3A. Clinicians must counsel their patients with epilepsy that the birth prevalence of any MCM in the general population is approximately 2.4%–2.9%, providing a comparison framework for their individual risk (Level A).

3B. Clinicians must consider using lamotrigine, levetiracetam, or oxcarbazepine in PWECP when appropriate based on the patient's epilepsy syndrome, likelihood of achieving seizure control, and comorbidities, to minimize the risk of MCMs (Level A).

3C. Clinicians must avoid the use of valproic acid in PWECP to minimize the risk of MCMs (composite outcome) or NTDs, if clinically feasible (Level A).

3D. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that the risk of any MCM is the highest with valproic acid as compared with other studied ASMs (Level A).

3E. To reduce the risk of cardiac malformations, clinicians must avoid the use of phenobarbital in PWECP, if clinically feasible (Level A).

3F. To reduce the risk of oral clefts, clinicians should avoid the use of phenobarbital and topiramate in PWECP, if clinically feasible (Level B).

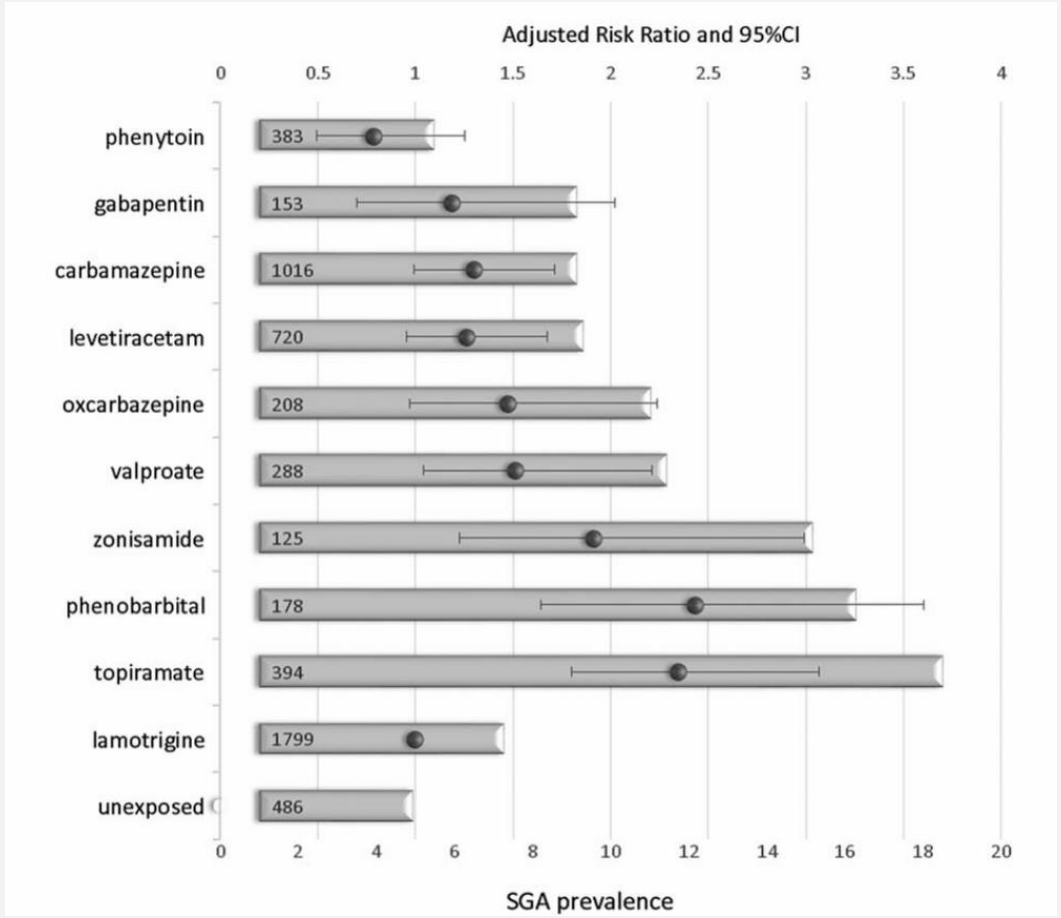
3G. To reduce the risk of urogenital and renal malformations, clinicians should avoid the use of valproic acid in PWECP, if clinically feasible (Level B).

3H. To enable early detection and timely intervention of MCMs, obstetricians should recommend fetal screening for MCMs (e.g., a detailed anatomical ultrasound, where available) for PWECP who are treated with any ASM during pregnancy (Level B).

3I. To enable early detection and timely intervention of congenital heart defects, obstetricians should recommend screening cardiac investigations of the fetus among PWECP who are treated with phenobarbital during pregnancy (Level B).

Neonatal Outcomes

Small gestational age



Hernandez-Diaz et al. *Ann Neurol.* 2017;82:457–465. 2. Pennel PB et al. *Epilepsy Behav.* 2012;24:449–456.

AAN – ASMs: Perinatal Outcomes

Recommendation 4 Statements

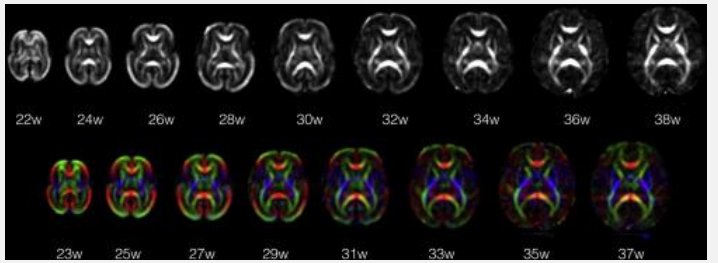
4A. Clinicians should counsel PWECP that the prevalence of intrauterine death does not differ among different ASM exposures in monotherapy (Level B).

4B. Clinicians should avoid the use of valproic acid or topiramate in PWECP to minimize the risk of offspring being born SGA, if clinically feasible (Level B).

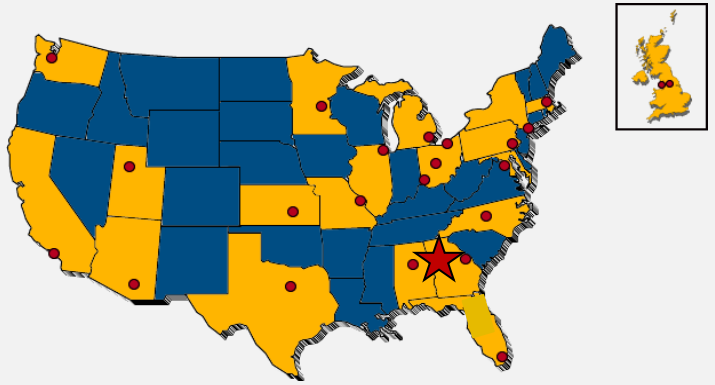
4C. To enable early identification of fetal growth restriction, obstetricians should recommend screening of fetal growth throughout pregnancy among PWECP who are treated with valproic acid or topiramate (Level B).

PREGNANCY

Neurodevelopmental Effects



NEAD (Neurodevelopmental Effects of Antiepileptic Drugs)



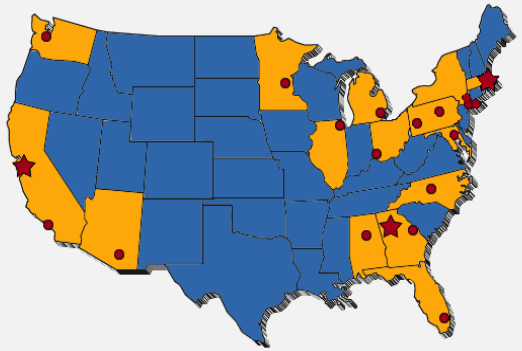
- Multicenter prospective, parallel-group observational study with statistical control
- 309 mother/child pairs, enrolled from late 1999 to early 2004, from 25 centers in USA & UK
- Antiepileptic drug (AED) monotherapy:
  - Carbamazepine (CBZ)
  - Lamotrigine (LTG)
  - Phenytoin (PHT)
  - Valproate (VPA)
- Blinded cognitive assessments: 2, 3, 4.5, & 6 years old
- Primary outcome: IQ at 6 years old

*NIH/NINDS #2RO1 NS 38455, NIH/NINDS #1 R01050659, UK Epilepsy Research Foundation #RB219738. IQ, intelligence quotient.
Meador KJ et al. NEJM 2009;360:1597–1605. Meador KJ et al. Lancet Neurol. 2013;12:244–52.

Maternal Outcomes & Neurodevelopmental Effects of Anti-Epileptic Drugs

MONEAD

Prospective, observational study, across 20 clinical sites



Multiple-PIs:
Kimford Meador, MD (Stanford)
Page B. Pennell, MD (University of Pittsburgh)

Obstetrics Core:
T. McElrath (BWH), M. Druzin (Stanford)

Neonatal Core: L. Van Marter (BWH) Semiology Core: J. French (NYU)
Mood Core: Z. Stowe (U Wisconsin)
OK Core: A. Birnbaum (U Minnesota)

Pregnant Women with Epilepsy (n=355), compared to 2 control groups:

Pregnant healthy controls (n=105)
Non-pregnant WWE (n=109)

Maternal Outcomes

- Seizures, OB complications, Depression

Children Outcomes

- Neurodevelopment, Neonatal complications, Breastfeeding

With PK modeling for level of exposure

Funded by NIH/NINDS,NICHD #U01-NS038455

Fetal Exposure to Valproate Associated With Lower IQ at Age 6

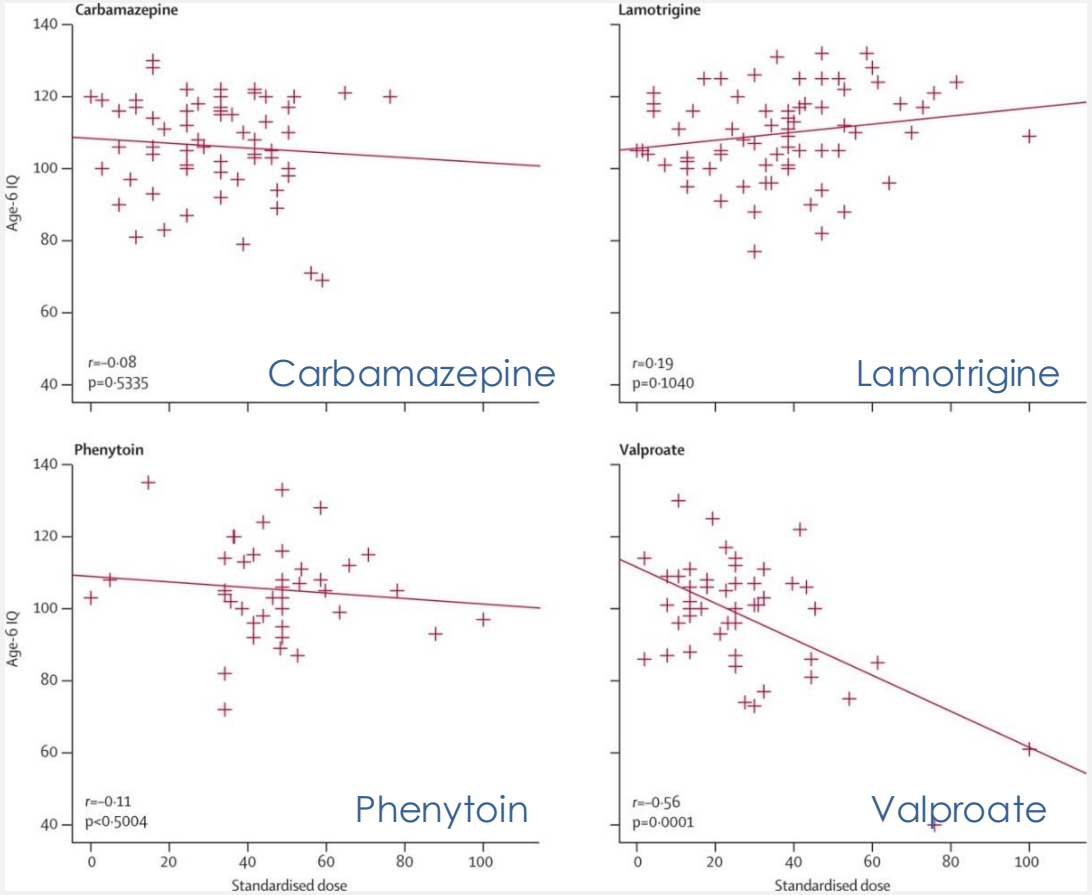
Mean IQs (95% Difference CIs from VPA) adjusted for maternal IQ, AED dose, gestational age and folate

	Carbamazepine	Lamotrigine	Phenytoin	Valproate
Total-enrolled				
Participants	94 (30%)	100 (32%)	55 (18%)	62 (20%)
Mean IQ*	105 (102–108)	108 (105–110)	108 (104–112)	97 (94–101)
Difference	7 (3–12)	10 (6–15)	10 (5–16)	NA
p value†	0·0015	0·0003	0·0006	NA
Age-6-completers				
Participants	61 (27%)	74 (33%)	40 (18%)	49 (22%)
Mean IQ*	106 (103–109)	108 (105–111)	109 (105–113)	98 (95–102)
Difference	8 (3–13)	10 (6–15)	11 (5–16)	NA
p value†	0·0010	0·0003	0·0004	NA

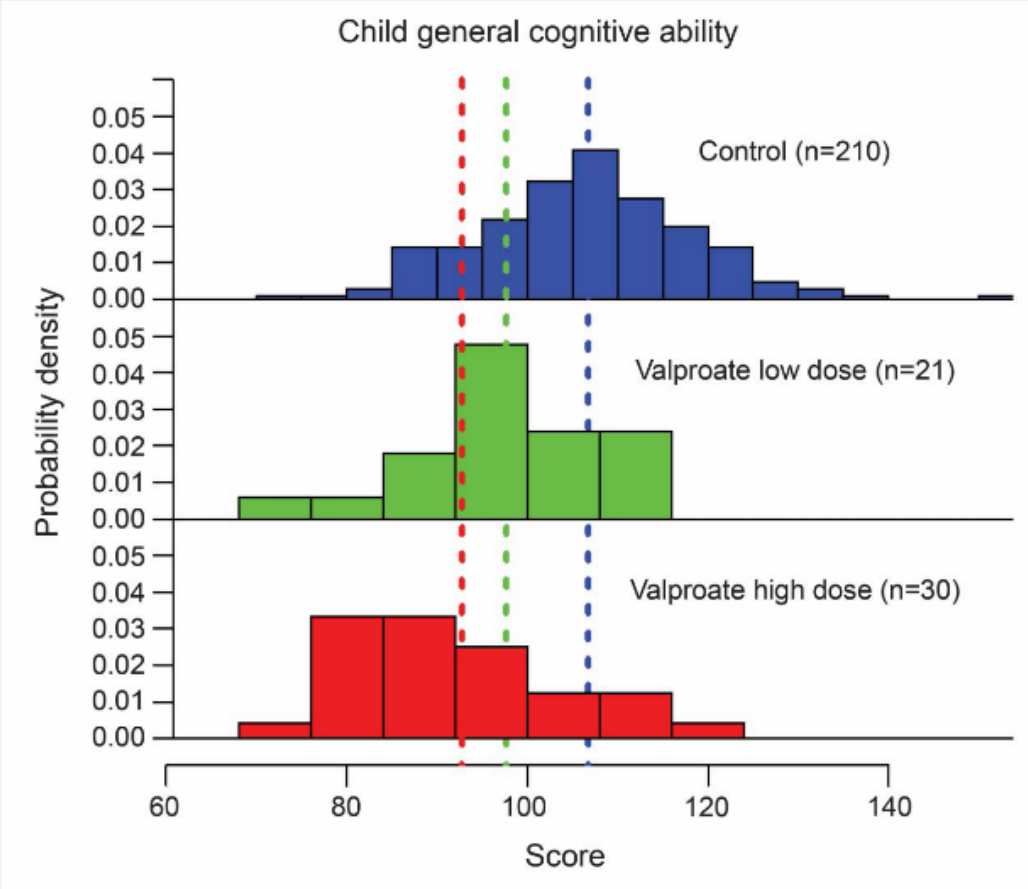
Meador KJ, et al. *Lancet Neurol*. 2013;12:244–252.

Dose-dependent IQ differences among VPA-exposed subject groups

NEAD study[1]



LMNDG study[2]



Colored dashed lines represent the mean IQ for each group.

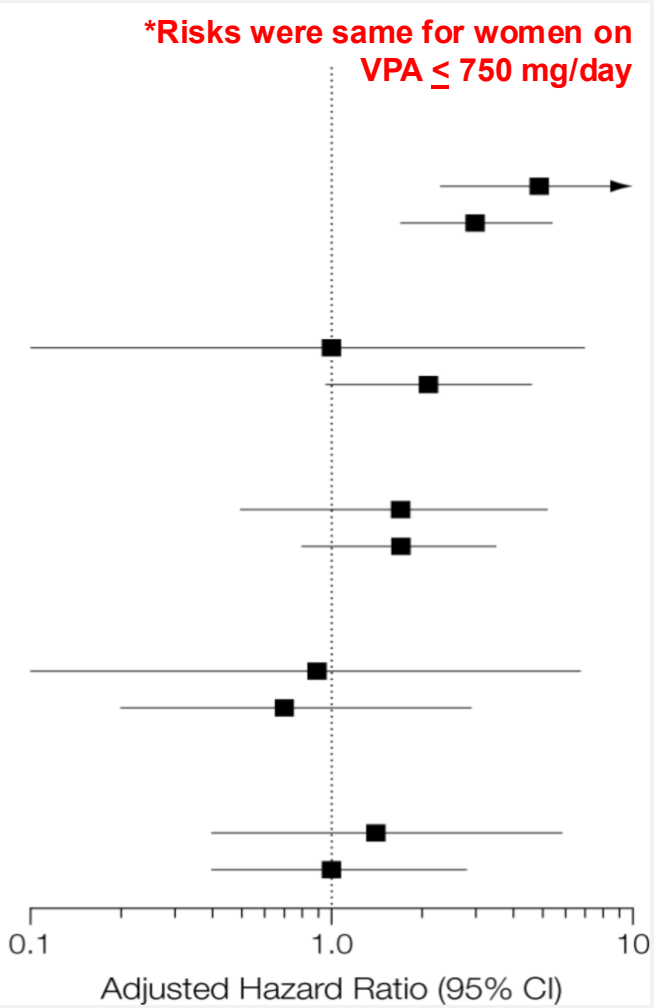
NEAD, Neurodevelopmental Effects of Antiepileptic Drugs. LMNDG, Neurodevelopmental Group
Meador KJ et al. Lancet Neurol 2013;12:244–52

Liverpool and Manchester

Baker G et al. Neurology 2015;84(4):382–390

Risk of autism with AED monotherapy

	No. Unexposed	No. Exposed	Adjusted Hazard Ratio (95% CI)
Valproate			
Total	655 107	388	
Childhood autism	2058	7	4.9 (2.3-10.3)
Autism spectrum disorder	5423	12	3.0 (1.7-5.4)
Oxcarbazepine			
Total	655 205	321	
Childhood autism	2064	1	1.0 (0.1-6.9)
Autism spectrum disorder	5427	7	2.1 (0.96-4.6)
Lamotrigine			
Total	654 747	647	
Childhood autism	2062	4	1.7 (0.5-5.2)
Autism spectrum disorder	5426	8	1.7 (0.8-3.5)
Clonazepam			
Total	655 233	269	
Childhood autism	2063	2	0.9 (0.1-6.7)
Autism spectrum disorder	5431	3	0.7 (0.2-2.9)
Carbamazepine			
Total	655 153	386	
Childhood autism	2065	2	1.4 (0.4-5.8)
Autism spectrum disorder	5433	4	1.0 (0.4-2.8)



AED, antiepileptic drugs; VPA, valproic acid.
Christensen J, et al. JAMA. 2013;309(16):1696–1703.

Fetal exposure to levetiracetam is not associated with a negative neurodevelopmental effect

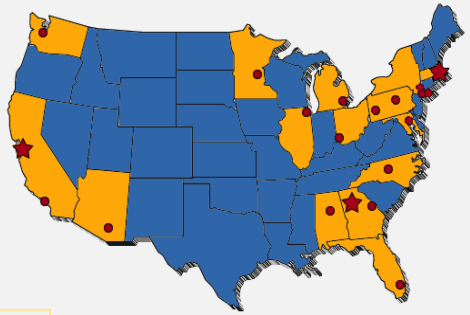
- Neuropsychological assessments were conducted between 5 and 9 years of age
- Adverse cognitive outcomes were not associated with increasing doses of LEV and TPM

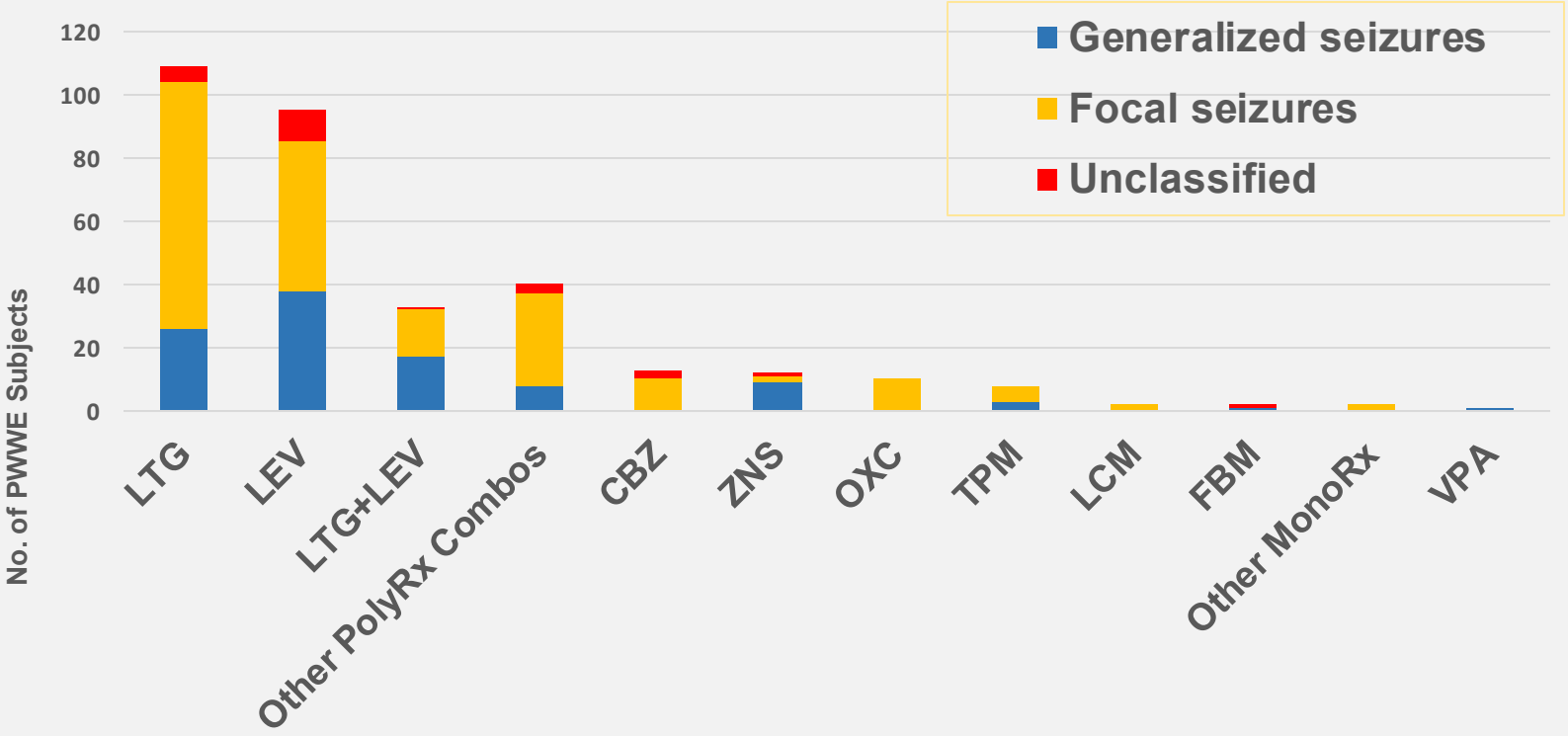
Table 2 Unadjusted means, standard errors, and rates below average performance by group for primary cognitive outcomes

	No medication (n = 55)		Gabapentin (n = 14)		Topiramate (n = 27)		Levetiracetam (n = 42)		Valproate (n = 47)	
WISC/WPPSI	Mean (SD)	No. (%) <85	Mean (SD)	No. (%) <85	Mean (SD)	No. (%) <85	Mean (SD)	No. (%) <85	Mean (SD)	No. (%) <85
Full-scale IQ	99.7 (13.6)	3 (6)	103.6 (12.9)	1 (8)	100.5 (13.2)	3 (12)	99.0 (13.6)	5 (12)	95.9 (14.1)	9 (19)
Verbal abilities	101.7 (13.0)	4 (7)	105.0 (12.6)	1 (7)	99.2 (11.2)	3 (11)	101.0 (11.2)	1 (2)	93.7 (14.6)	10 (21)
Nonverbal abilities	100.8 (14.6)	6 (11)	104.3 (14.2)	1 (7)	102.4 (14.7)	3 (11)	99.6 (13.8)	7 (17)	101.5 (14.7)	6 (13)
Processing speed	97.1 (12.5)	8 (15)	103.6 (9.7)	0 (0)	100.0 (13.3)	3 (11)	94.7 (12.6)	7 (17)	94.6 (11.9)	8 (17)

LEV, levetiracetam; LTG, lamotrigine; PHT, phenytoin; VPA, valproate; DCI, confidence intervals for difference from VPA.
Bromley RL et al. Neurology. 2016;87(18):1943–1953.

Prescribing Patterns in PWWE at MONEAD sites





Meador KJ, Pennell PB, May RC, Gerard E, Kalayjian L, Velez-Ruiz N, Penovich P, Cavitt J, French J, Hwang S, Pack A, Sam M, Moore E, Ippolito DM, MONEAD Investigator Group. *Epilepsy & Behavior* 2018.

Cognitive outcomes at age 3 years in children with fetal exposure to antiseizure medications (MONEAD study) in the USA: a prospective, observational cohort study

*Kimford J Meador, Morris J Cohen, David W Loring, Abigail G Matthews, Carrie Brown, Chelsea P Robalino, Angela K Birnbaum, Paula E Voinescu, Laura A Kalayjian, Elizabeth E Gerard, Evan R Gedzelman, Julie Hanna, Jennifer Cavitt, Maria Sam, Jacqueline A French, Sean Hwang, Alison M Pack, Page B Pennell, for the MONEAD Investigator Group**

Lancet Neurol 2023; 22: 712–22

See Comment page 648

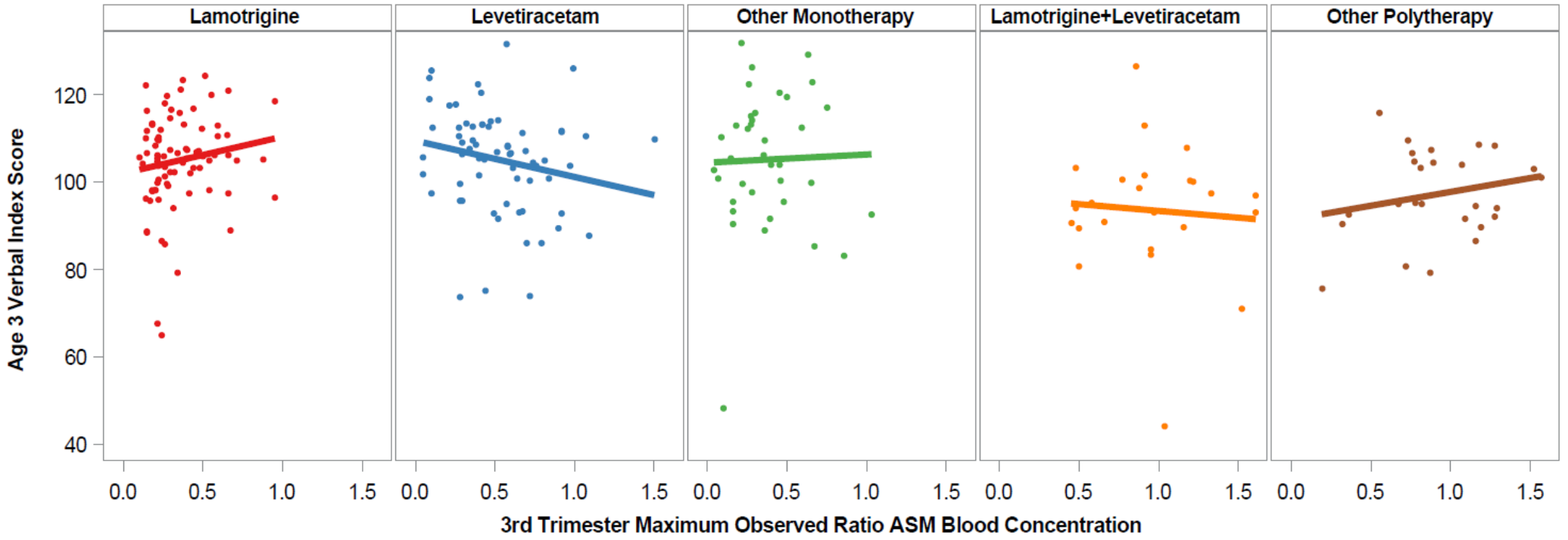
*Members listed in appendix

Summary

Background The neurodevelopmental effects of fetal exposure to most antiseizure medications are unclear. We aimed to investigate the effects of fetal exposure to commonly used antiseizure medications on neuropsychological outcomes at age 3 years.

Interpretation We found no difference in neurodevelopmental outcomes between children with fetal exposure to newer antiseizure medications compared with unexposed children. However, some exposure-dependent antiseizure medication effects were seen in secondary analyses. The adverse effects of maternal post-birth anxiety emphasise the importance of screening mothers during pregnancy and postpartum and implementing interventions. Additional studies are needed to clarify the exposure-dependent effects.

Exposure-dependent effects on the verbal index scores



Concentration-dependent in the third trimester!

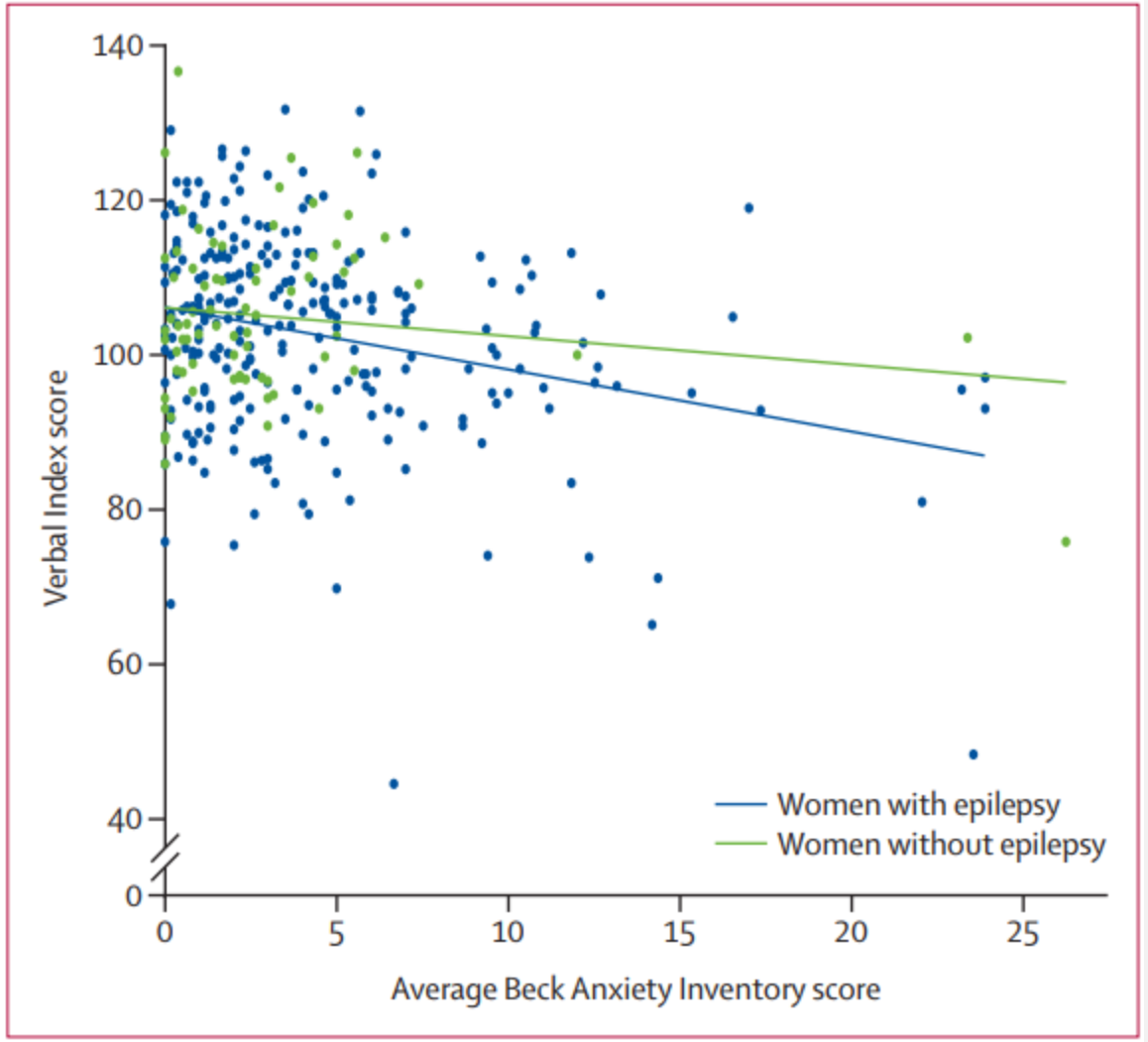


Figure 2: **Scatter plots of Verbal Index scores in children at age 3 years compared with maternal post-birth average Beck Anxiety Inventory scores for children of women with epilepsy and women without epilepsy**

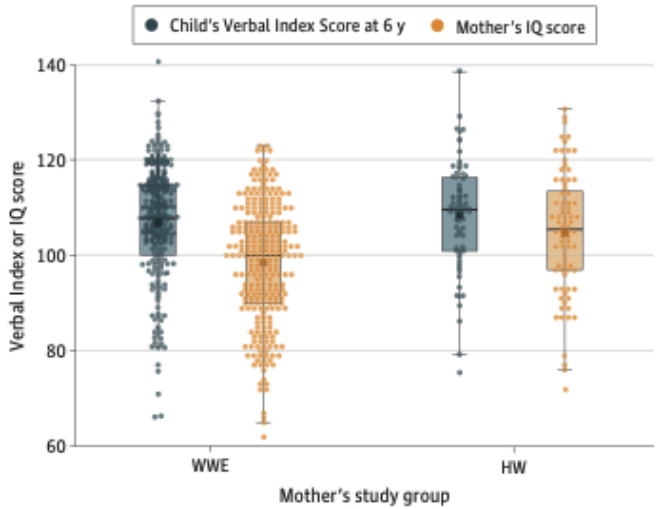
JAMA Neurology | Original Investigation

Neuropsychological Outcomes in 6-Year-Old Children of Women With Epilepsy

A Prospective Nonrandomized Clinical Trial

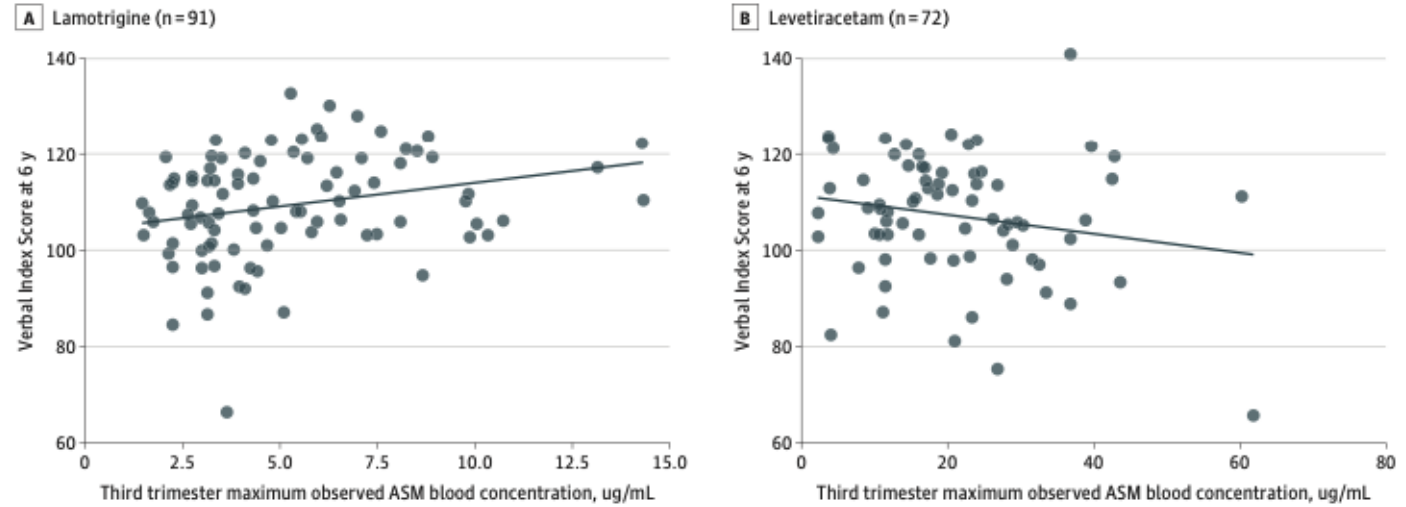
JAMA Neurol. 2025;82(1):30-39. doi:10.1001/jamaneurol.2024.3982
Published online November 25, 2024.

Figure 1. Verbal Index Score in 6-Year-Old Children and Mother's IQ by Mother's Study Group—Children of Women With Epilepsy (WWE) vs Healthy Women (HW) (N = 353)



The bold dot represents the mean, the middle bar is the median, the lower and upper bars of the box represent the 1st and 3rd quartile, respectively, the bottom and top of the whiskers are the most extreme points less than or equal to 1.5 times the IQR, and the dots outside the whiskers are points that are more than ±1.5 times the IQR. Children aged 6 years with imputed Verbal Index Scores excluded from figure.

Figure 2. Scatter Plot of Verbal Index Score in 6-Year-Old Children vs Third-Trimester Maximum Observed Antiseizure Medication (ASM) Blood Concentration for Lamotrigine and Levetiracetam in Children of Women With Epilepsy (WWE) With Third Trimester Blood Concentrations



Other important recent neurodevelopmental studies

Research

JAMA Neurology | Original Investigation

Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability

Marte-Helene Bjørk, MD, PhD; Helga Zoega, PhD; Maarit K. Leinonen, MD, PhD; Jacqueline M. Cohen, PhD; Julie Werenberg Dreier, PhD; Kari Furu, PhD; Nils Erik Gilhus, MD, PhD; Mika Gissler, PhD; Óskar Hálfdánarson, PhD; Jannicke Igland, PhD; Yuelian Sun, PhD; Torbjörn Tomson, MD, PhD; Silje Alvestad, MD, PhD; Jakob Christensen, MD, PhD

IMPORTANCE Women with epilepsy frequently need antiseizure medication (ASM) to prevent seizures in pregnancy. Risk of neurodevelopmental disorders after prenatal exposure to AMSs is uncertain.

OBJECTIVE To determine whether children exposed prenatally to ASMs in monotherapy and duotherapy have increased risk of neurodevelopmental disorders.

DESIGN, SETTING, AND PARTICIPANTS The Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED) is a population-based cohort study using health register and social register data from Denmark, Finland, Iceland, Norway, and Sweden (1996-2017; analysis performed February 2022). From 4 702 774 alive-born children with available mother-child identities and maternal prescription data, this study included 4 494 926 participants. Children from a multiple pregnancy or with chromosomal disorders or uncertain pregnancy length were excluded (n = 207 848).

EXPOSURES Prenatal exposure to ASM determined from maternal prescription fills between last menstrual period and birth.

MAIN OUTCOMES AND MEASURES We estimated cumulative incidence at age 8 years in exposed and unexposed children. Cox regression adjusted for potential confounders yielded adjusted hazard ratios (aHRs) with 95% CIs for autism spectrum disorder (ASD), intellectual disability (ID), or any neurodevelopmental disorder (ASD and/or ID).

RESULTS A total of 4 494 926 children were included; 2 306 993 (51.3%) were male, and the median (IQR) age at end of follow-up was 8 (4.0-12.1) years. Among 21 634 unexposed children of mothers with epilepsy, 1.5% had a diagnosis of ASD and 0.8% (numerators were not available because of personal data regulations in Denmark) of ID by age 8 years. In same-aged children of mothers with epilepsy exposed to topiramate and valproate monotherapy, 4.3% and 2.7%, respectively, had ASD, and 3.1% and 2.4% had ID. The aHRs for ASD and ID after topiramate exposure were 2.8 (95% CI, 1.4-5.7) and 3.5 (95% CI, 1.4-8.6), respectively, and after valproate exposure were 2.4 (95% CI, 1.7-3.3) and 2.5 (95% CI, 1.7-3.7). The aHRs were elevated with higher ASM doses compared with children from the general population. The duotherapies levetiracetam with carbamazepine and lamotrigine with topiramate were associated with increased risks of neurodevelopmental disorders in children of women with epilepsy: levetiracetam with carbamazepine: 8-year cumulative incidence, 5.7%; aHR, 3.5; 95% CI, 1.5-8.2; lamotrigine with topiramate: 8-year cumulative incidence, 7.5%; aHR, 2.4; 95% CI, 1.1-4.9. No increased risk was associated with levetiracetam with lamotrigine (8-year cumulative incidence, 1.6%; aHR, 0.9; 95% CI, 0.3-2.5). No consistently increased risks were observed for neurodevelopmental disorders after prenatal exposure to monotherapy with lamotrigine, levetiracetam, carbamazepin, oxcarbazepine, gapapentin, pregabalin, clonazepam, or phenobarbital.

CONCLUSIONS AND RELEVANCE In this cohort study, prenatal exposure to topiramate, valproate, and several duotherapies were associated with increased risks of neurodevelopmental disorders.

Multimedia

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Topiramate has significant negative neurodevelopmental effects

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Adaptive behaviour in children exposed to topiramate in the womb: An observational cohort study

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ABSTRACT

Objective: Many women with epilepsy need to continue anti-seizure medications (ASMs) throughout pregnancy. The current study investigated adaptive behaviour outcomes in children exposed to topiramate in the womb.
Method: An observational, cross-sectional study was designed, recruiting mother-child-pairs from the UK Epilepsy and Pregnancy Register (UKEPR). Health, developmental histories and Vineland Adaptive Behaviour Scale-Third Edition (VABS-III) assessments were administered via telephone by a blinded researcher, supplemented with prospectively collected pregnancy and medication information. Topiramate monotherapy exposed children were compared to VABS-III normative data as recruitment was disrupted by the COVID-19 pandemic.
Results: Thirty-four women with epilepsy from 135 (25%) initially agreed to participate in the study, of whom 26 women completed telephone interviews about their children ($n = 28$). Children ranged from 2.5 to 17 years of age at the time of assessment. Six topiramate-exposed children were born small for gestational age, and there were significant associations between birthweight, dose and VABS-III scores. Significantly lower scores were observed in topiramate-exposed children ($n = 21$) with a significant dose-response relationship established after adjustment for parental educational level. Daily mean dosage was 280.21 mg, with high dosages of topiramate associated with a 12-point reduction in VABS-III scores. Additionally, four topiramate-exposed children (19.05%) had diagnoses of Autism Spectrum Disorder, which was significantly higher than UK prevalence rates (1.1%).
Conclusions: The findings of poorer adaptive behaviour, higher incidence of ASD and associations with birth weight are of concern and require further validation and replication using larger prospectively-recruited samples and comparator cohorts. Implications for research and clinical practice are discussed.

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Risk of Autism after Prenatal Topiramate, Valproate, or Lamotrigine Exposure

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BACKGROUND

Maternal use of valproate during pregnancy has been associated with an increased risk of neurodevelopmental disorders in children. Although most studies of other antiseizure medications have not shown increased risks of these disorders, there are limited and conflicting data regarding the risk of autism spectrum disorder associated with maternal topiramate use.

METHODS

We identified a population-based cohort of pregnant women and their children within two health care utilization databases in the United States, with data from 2000 through 2020. Exposure to specific antiseizure medications was defined on the basis of prescription fills from gestational week 19 until delivery. Children who had been exposed to topiramate during the second half of pregnancy were compared with those unexposed to any antiseizure medication during pregnancy with respect to the risk of autism spectrum disorder. Valproate was used as a positive control, and lamotrigine was used as a negative control.

RESULTS

The estimated cumulative incidence of autism spectrum disorder at 8 years of age was 1.9% for the full population of children who had not been exposed to antiseizure medication (4,199,796 children). With restriction to children born to mothers with epilepsy, the incidence was 4.2% with no exposure to antiseizure medication (8815 children), 6.2% with exposure to topiramate (1030 children), 10.5% with exposure to valproate (800 children), and 4.1% with exposure to lamotrigine (4205 children). Propensity score–adjusted hazard ratios in a comparison with no exposure to antiseizure medication were 0.96 (95% confidence interval [CI], 0.56 to 1.65) for exposure to topiramate, 2.67 (95% CI, 1.69 to 4.20) for exposure to valproate, and 1.00 (95% CI, 0.69 to 1.46) for exposure to lamotrigine.

CONCLUSIONS

The incidence of autism spectrum disorder was higher among children prenatally exposed to the studied antiseizure medications than in the general population. However, after adjustment for indication and other confounders, the association was substantially attenuated for topiramate and lamotrigine, whereas an increased risk remained for valproate. (Funded by the National Institute of Mental Health.)

AAN – ASMs: Neurodevelopmental Outcomes

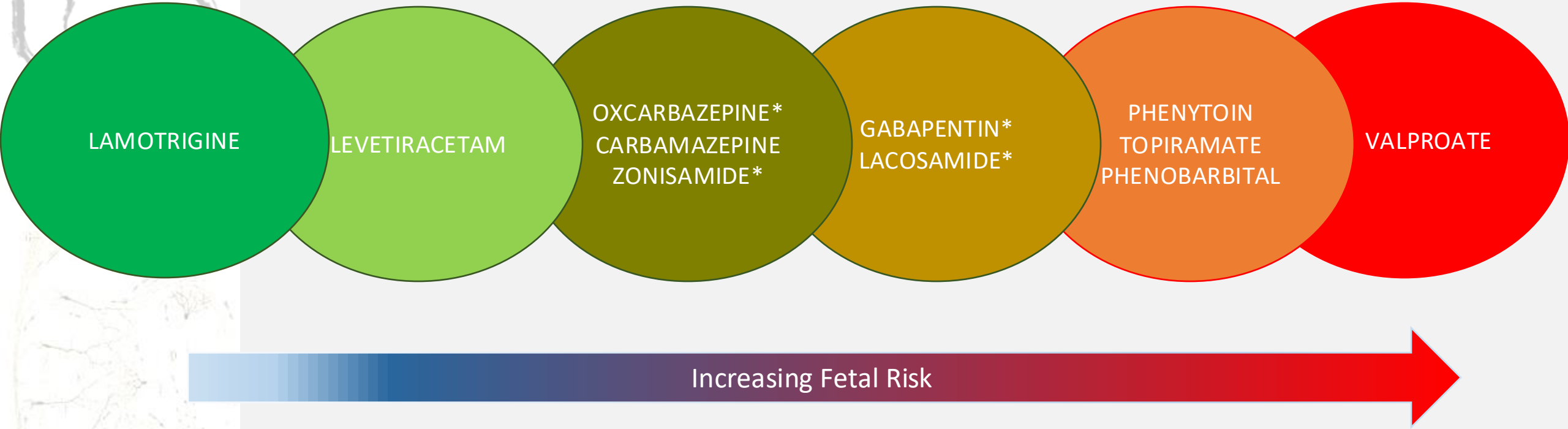
5A. To reduce the risk of poor neurodevelopmental outcomes, including ASD and lower IQ, in children born to PWECP, clinicians must avoid the use of valproic acid in PWECP, if clinically feasible (Level A).

5B. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that in utero exposure to valproic acid is likely or possibly associated with a decrease in full scale, verbal, and non-verbal IQ, as compared with other studied ASMs (i.e., carbamazepine, gabapentin, lamotrigine, levetiracetam, phenytoin, and topiramate) (Level A).

5C. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that in utero exposure to valproic acid is possibly associated with an increased risk of ASD as compared with other studied ASMs (i.e., carbamazepine, clonazepam, levetiracetam, and lamotrigine) (Level A).

5D. Clinicians should implement age-appropriate developmental screening in children exposed to any ASM in utero born to PWECP (Level B).

My Current Preferential selection of AEDs for WWE of childbearing age



Suggestions for the management of pregnant women with epilepsy

- 1st TM: Re-dosing if vomiting within 1h, ensure they have Ob/MFM care
- 2nd TM: Detailed structural US
- 3rd TM: Peripartum and postpartum issues
  - Dose AEDs accurately and have the patient bring her medications to the hospital (same time/formulation)
  - Epidural anesthesia recommended to allow some periods of less than maximal intensity of physical stressors during labor and delivery
  - Lorazepam/IV AEDS should be available during labor and delivery as needed for acute seizure control
  - Do not neglect psychiatric needs

Voinescu PE and Pennell PB. *Semin Neurol* 2017

POSTPARTUM

- Seizure provoking factors
- Pharmacokinetic considerations
- Breastfeeding

Summary ASM exposure via breastmilk

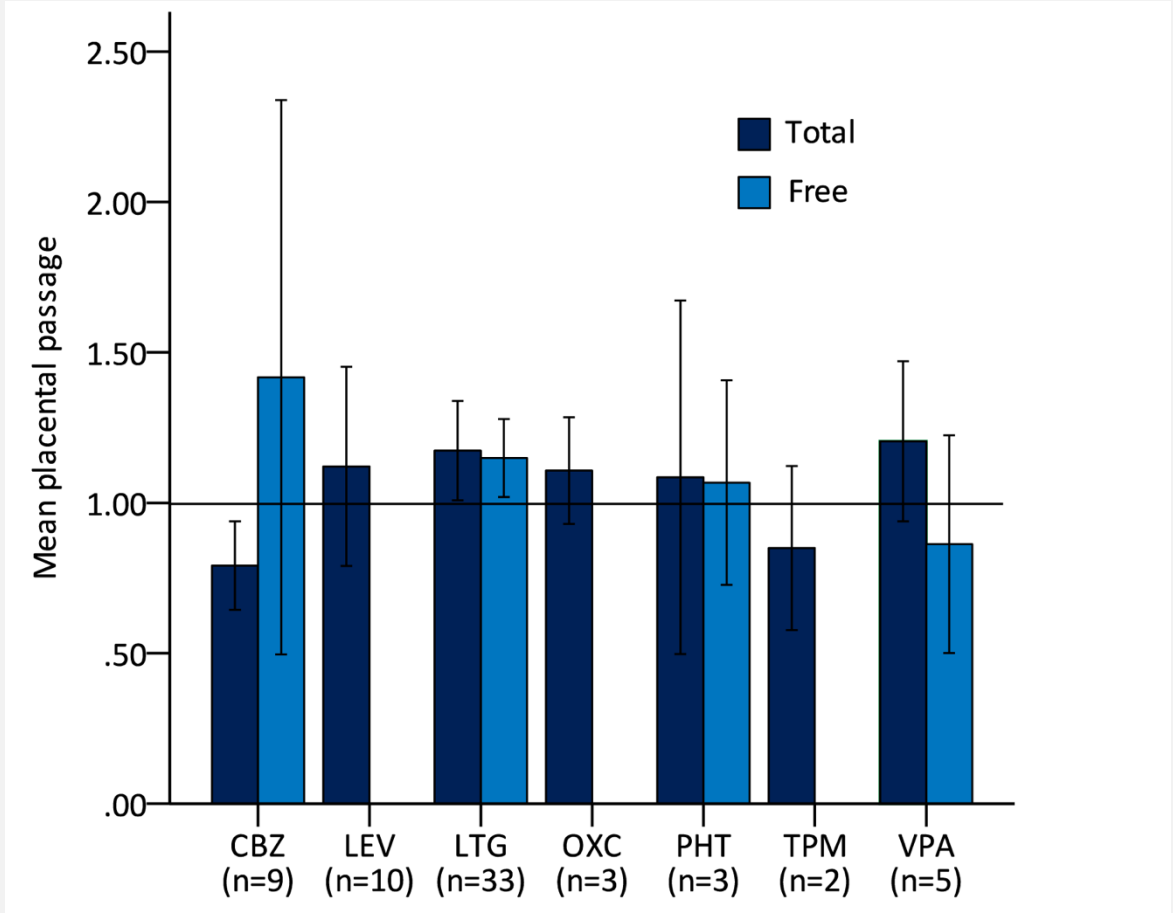
- The degree of penetration into breast milk varies for different ASMs
  - Some penetrate in potentially clinically important amounts: PRM, LEV, GBP, LTG, TPM
  - Others less so: VPA, PB, PHT, CBZ
- Significantly lower exposure than in utero (MONEAD data)

ASM, antiseizure medication; CBZ, carbamazepine; GBP, gabapentin; IQ, intelligence quotient; LEV, levetiracetam; LTG, lamotrigine; NEAD, neurodevelopmental effects of antiepileptic drugs; MONEAD, maternal outcomes and neurodevelopmental effects of antiepileptic drugs; PB, phenobarbital; PHT, phytoin; PRM, primidone; TPM, topiramate; VPA, valproic acid.

Meador, et al. JAMA Pediatr. 2014;168(8):729–736.

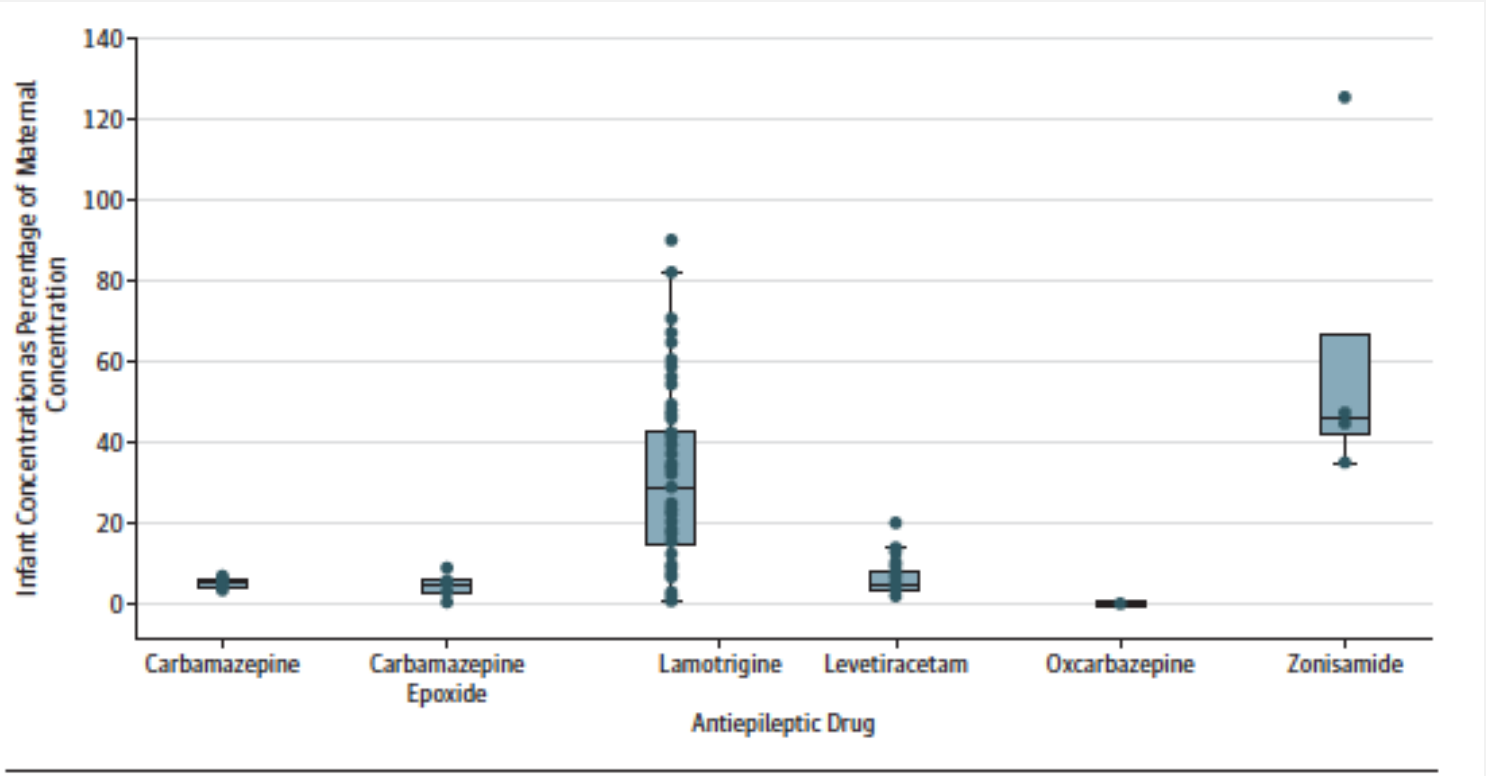
Mean placental passage of ASMs

(Umbilical Cord/Maternal blood venous samples)



Bank, Stowe, Newport, Pennell, *Epilepsia* 2017.

Percentage of infant to mother plasma concentrations



Box plots represent 25%ile and 75%ile.

40 /54 infants exposed to LEV were < LLoQ.

Birnbaum A, MONEAD, *JAMA Neuro*, Dec 30, 2019.

Neurodevelopmental effects of ASMs through breastmilk

- NEAD study and breastfeeding: Age 6 year-old cognitive outcomes
  - 44% of children were breastfed
  - Mean adjusted IQ scores:
    - 4 IQ points higher in the BF group
    - Higher verbal abilities

NEAD, neurodevelopmental effects of antiepileptic drugs
Meador, et al. *JAMA Pediatr.* 2014;168(8):729–736.

Suggestions for delivery/postpartum period

- Dose ASMs accurately
- Have the patient bring her medications to the hospital (same time/formulation)
- Epidural anesthesia recommended; allows periods of less than maximal intensity of physical stressors during labor and delivery
- Lorazepam/IV ASMs should be available during labor and delivery as needed for acute seizure control
- Risk for seizures may be increased peripartum (sleep deprivation)
- Postpartum ASM tapers are established based on individual factors
- Breastfeeding is supported, with possible neurodevelopmental benefits, but with implementation of strategies to lessen sleep deprivation
- Counseling about signs of depression and action plans if symptoms develop
- Safety precautions with the newborn (no co-sleeping, bathing the baby alone)
- Confirm postpartum contraception

ASM, antiseizure medication; IV, intravenous.
Voinescu PE and Pennell PB. *Semin Neurol* 2017;37:611–623.

THANK YOU!